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(54) Title: **NEUROPILIN/VEGF C/VEGFR 3 MATERIALS AND METHODS**

(57) Abstract: The present invention relates to identifying modulators of VEGF-C or VEGF-D ligand binding to the nervous system transmembrane protein neuropilin-2 and materials and methods for detecting said modulators.

## NEUROPILIN/VEGF-C/VEGFR-3 MATERIALS AND METHODS

### FIELD OF THE INVENTION

The present invention provides materials and methods relating to  
5 cellular and molecular biology and medicine, particularly in the areas of  
vascularization and angiogenesis and the interactions of the vascular system with the  
nervous system.

### BACKGROUND OF THE INVENTION

10 Interactions of the neuropilin receptor proteins with their ligands in the  
collapsin/semaphorin family of molecules promotes development of neuronal growth  
cones and axon guidance, the process which regulates the paths of extending axons  
during the development of neuronal tissue. Improper retraction of the neural growth  
cones leads to excess, unwanted innervation of tissue.

15 Collapsin/semaphorin proteins belong to a family of molecules  
containing a characteristic semaphorin domain of approximately 500 amino acids in  
the amino terminus. Over 20 members of the semaphorin family are currently known,  
both secreted and membrane bound forms, which can be divided into six different  
subgroups based on primary protein structure. Both secreted and membrane bound  
20 semaphorins bind to their receptors as disulfide linked homodimers, and the  
cytoplasmic tail of membrane bound semaphorins can induce clustering of these  
ligands in the cell membrane.

Class III semaphorins, secreted proteins which contain the semaphorin  
domain followed by a C2-type immunoglobulin like domain, have been found to be  
25 integrally involved in the repulsion and collapse of neuronal growth cones, a process  
which prevents improper innervation of dorsal root ganglia, sympathetic neurons, and  
both cranial and spinal neurons.

Recently, two receptors for the class III semaphorins were identified,  
neuropilin-1(NRP-1) (Kolodkin et al, Cell. 90:753-762. 1997 and He et al, Cell.  
30 90:739-51. 1997) and neuropilin-2 (NRP-2) (Chen et al, Neuron, 19:547. 1997).  
Neuropilin-1, a type-I membrane protein originally isolated from the *Xenopus*

nervous system, was identified by semaphorin III receptor expression cloning, as a high affinity receptor for Sema III and other semaphorin family members. Further analysis by PCR using sequences homologous to neuropilin-1 identified a related receptor, neuropilin-2, which shows approximately 44% homology to NRP-1  
5 throughout the entire protein length.

The extracellular portion of both NRP-1 and NRP-2 shows an interesting mix of cell binding domains, possessing five distinct protein domains designated a1/a2, b1/b2, and c. The a1/a2 (CUB) domains resemble protein sequences found in complement components C1r and Cs while the b1/b2 domains are  
10 similar to domains found in coagulation factors V and VIII. The central portion of the c domain, similar to the meprin/A5/mu-phosphatase (MAM) homology domain, is important for neuropilin dimerization. The intracellular region of neuropilins contains a transmembrane domain and a short, highly conserved cytoplasmic tail of ~43 amino acids that possesses no known catalytic activity to date. Both the a1/a2 and b1/b2  
15 domains are necessary to facilitate semaphorin binding to neuropilins.

Since the short cytoplasmic tail of neuropilins does not possess signaling capabilities, neuropilins probably couple with other receptors to transmit intracellular signals as a result of semaphorin binding. Investigation of this scenario concluded that neuropilins interact with another family of semaphorin receptors, the  
20 plexins, which possess a cytoplasmic tail containing a sex-plexin domain capable of undergoing phosphorylation and initiating downstream signaling cascades (Tamagnone et al Trends in Cell Biol, 10:377-83. 2000). Plexins were originally isolated as orphan receptors for membrane bound semaphorins, and plexins alone are incapable of binding secreted semaphorins such as those in the class III subfamily. A  
25 great deal of evidence now demonstrates that class III semaphorin binding is mediated through a receptor complex which includes homo- or heterodimeric neuropilins and a plexin molecule needed to transduce intracellular signals. Interactions of plexins with neuropilins confers specificity of semaphorin binding and can also increase the binding affinity of these ligands. Signaling of semaphorins through their receptors is  
30 reviewed in Fujisawa et al, (Current Opinion in Neurobiology, 8:587. 1998) and Tamagnone et al, (Trends in Cell Biol, 10:377. 2000).

Neuropilin-1 (Tagaki et al., Neuron 7:295-307. 1991; Fujisawa et al., Cell Tissue Res. 290:465-70. 1997), a 140 kD protein whose gene is localized to

chromosome 10p12 (Rossingnol et al., Genomics 57:459-60. 1999), is expressed in a wide variety of tissues during development, including nervous tissue, capillaries and vessels of the cardiovascular system, and skeletal tissue, and persists in many adult tissues, most notably the placenta and heart. In addition to binding Sema3A, NRP-1  
 5 also binds several other semaphorin family members including Sema3B, Sema3C (SemaE), and Sema3F (SemaIV) (with low affinity) (He et al., Cell 90:739-51. 1997; Kolodkin et al., Cell 90:753-62. 1997). Mice homozygous mutant at the NRP-1 locus demonstrate defects not only in axonal guidance but also show altered vascularization in the brain and defects in the formation of large vessels of the heart (Kawasaki et al,  
 10 Development 126:4895. 1990). Interestingly, NRP-1 overexpression in embryos leads to excess capillary and vessel formation and hemorrhaging, implicating a role for NRP-1 in vascular development (Kitsukawa et al, Development, 121:4309. 1995).

Recent evidence shows that neuropilin-1 can act as a receptor for an isoform of vascular endothelial growth factor (VEGF/VEGF-A) (Soker et al, Cell  
 15 92:735. 1998), which is a key mediator of vasculogenesis and angiogenesis in embryonic development (reviewed in Robinson et al, J. Cell Science. 114:853-65) and also plays a significant role in tumor angiogenesis. Binding of VEGF to receptor tyrosine kinases (RTK) VEGFR-1 and VEGFR-2 facilitates vascular development. Both the non-heparin dependent VEGF<sub>121</sub> isoform and the heparin-binding VEGF<sub>165</sub>  
 20 bind VEGFR-2 with the same affinity in vitro, but do not elicit equivalent biochemical responses, indicating that additional factors mediate VEGFR-2 activation (Whitaker et al, J Bio Chem. 276:25520-31. 2001). Analysis of the binding of several splice variants of VEGF reveal that NRP-1 does not bind the VEGF<sub>121</sub> isoform but selectively binds the VEGF<sub>165</sub> variant in a heparin- dependent manner within the b  
 25 domain of NRP-1 (Giger et al, Neuron 21:1079-92. 1998). NRP-1 demonstrates a binding affinity for the VEGF<sub>165</sub> isoform comparable to that of it's Sema3A ligand. This differential affinity of NRP-1 for VEGF<sub>165</sub> may explain the signaling capabilities of this splice variant over the non-heparin binding VEGF<sub>121</sub> and may indicate that neuropilin-1 interacts with VEGFR-2 as a co-receptor in VEGF binding (Whitaker et  
 30 al., 2001), similar to its role in plexin/semaphorin complexes. VEGF<sub>165</sub> binds NRP-1 through VEGF exon 7, which confers heparin binding affinity to this molecule, and is lacking in the VEGF<sub>121</sub> isoform. NRP-1 also binds other VEGF family members,



VEGF-B and placenta growth factor (PlGF-2) (Migdal et al, J. Biol.Chem. 273:22272-78. 1998; Makinen et al, J. Biol. Chem. 274: 21217-222. 1999).

Neuropilin-2 (Chen et al, Neuron 19:547-59. 1997), a 120 kD protein whose gene is localized to chromosome 2q34 (Rossingnol et al., Genomics 57:459-60. 1999), exhibits similar tissue distribution in the developing embryo as neuropilin-1, but does not appear to be expressed in endothelial cells of capillaries (Chen et al, Neuron 19:547-59. 1997). NRP-2 is also a semaphorin receptor, binding Sema3F with high affinity, Sema3C with affinity comparable to Sema3C/NRP-1 binding, NRP-2 also appears to interact with very low affinity to Sema3A (Kolodkin et al., Cell 90:753-62. 1997). NRP-2 deficient mice survive embryogenesis with no apparent vascular defects, but exhibit defects in the Sema3F-dependent formation of sympathetic and hippocampal neurons and defects in axonal projections in the peripheral and central nervous systems, implicating NRP-2 in axonal guidance (Chen et al, Neuron 25:43-56. 2000; Giger et al, Neuron 25:29-41. 2000) and suggesting distinct roles for NRP-1 and NRP-2 in development. NRP-2 expression has also been noted in sites that innervate smooth muscle cells such as mesentery, muscular, and submucosal plexuses (Cohen et al, Biochem Biophy Res Comm. 284:395-403. 2001).

Experimental evidence establishes that, similar to NRP-1, neuropilin-2 preferentially binds VEGF<sub>165</sub>, and shows additional binding to the VEGF<sub>145</sub> isoform, another heparin-binding splice variant of VEGF (Gluzman-Poltorak et al, J. Biol Chem. 275:18040-45. 2000). Neuropilin-2 interaction with the VEGF<sub>145</sub> splice variant, which lacks exon 7, is mediated through VEGF<sub>145</sub> exon 6 which, like exon 7, is capable of mediating heparin binding activity. VEGF<sub>145</sub> cannot bind NRP-1, which further supports the theory of differential functions for neuropilin-1 and neuropilin-2 in vascular development. VEGF<sub>145</sub> was originally isolated from carcinomas of the female reproductive tract (Pavelock et al, Endocrinology. 142: 613-22. 2001) where neuropilin-2 expression shows differential regulation in response to hormonal changes as compared to NRP-1 and VEGFR-2. The co-expression of both neuropilins, VEGFs, and VEGFRs in a particular cell type may be indicative of a potential receptor/ligand complex formation and needs to be investigated in greater detail.

VEGF/VEGFR interactions play an intergral role in embryonic vasculogenesis and angiogenesis, as well as a role in adult tissue neovascularization during wound healing, remodeling of the female reproductive system, and tumor

growth. Elucidating additional factors involved in the regulation of neovascularization and angiogenesis, as well as their roles in such processes, would aid in the development of therapies directed toward prevention of vascularization of solid tumors and induction of tumor regression, and induction of vascularization to promote faster, more efficient wound healing after injury, surgery, or tissue transplantation, or to treat ischemia by inducing angiogenesis and arteriogenesis of vessels that nourish the ischemic tissue. In fact, modulation of angiogenic processes may be instrumental in treatment or cure of many of the most significant diseases that plague humans in the developed world, such as cerebral infarction/bleeding, acute myocardial infarction and ischemia, and cancers. Modulation of neuronal growth also is instrumental in treatment of numerous congenital, degenerative, and trauma-related neurological conditions. The newfound interaction between neuropilins and VEGF provided one target for intervention at a molecular level for both neuronal and vascular diseases and conditions. However, the ability to develop targeted therapies is complicated by the existence of multiple binding partners for neuropilins. There exists a need to delineate molecules that bind neuropilins in order to permit identification of modulation of neuropilin activities and to optimize the specificity of such molecules to optimize therapies in areas of unwanted angiogenesis, as in cancers or solid tumor growth, and potentiate pro-angiogenic properties to promote and speed needed blood vessel growth, as in wound healing; and optimize therapies directed to neuronal growth and organization.

### SUMMARY OF THE INVENTION

The present invention addresses one or more needs in the art relating to modulation of angiogenic and nervous system growth and function, by identifying novel molecular interactions between neuropilins and VEGF-C molecules, and between neuropilins and VEGFR-3 molecules. These newly delineated interactions facilitate identification of novel materials and methods for modulating both angiogenic processes (including lymphangiogenic processes) and processes involved in neural cell regeneration. The newly delineated interactions also facilitate better therapeutic targeting by permitting design of molecules that modulate single receptor-ligand interactions highly selectively, or molecules that modulate multiple interactions.

For example, the discovery of VEGF-C-neuropilin interactions provides novel screening assays to identify new therapeutic molecules to modulate (up-regulate/activate/stimulate or downregulate/inhibit) VEGF-C-neuropilin interactions. Such molecules are useful as therapeutics (and/or as lead compounds) for diseases and conditions in which VEGF-C/neuropilin interactions have an influence, including those in which lymphatic or blood vessel growth play a role.

In one embodiment, the invention provides a method for identifying a modulator of binding between a neuropilin receptor and VEGF-C polypeptide comprising steps of:

- 10 a) contacting a neuropilin composition that comprises a neuropilin polypeptide with a VEGF-C composition that comprises a VEGF-C polypeptide, in the presence and in the absence of a putative modulator compound;
- b) detecting binding between neuropilin polypeptide and VEGF-C polypeptide in the presence and absence of the putative modulator; and
- 15 c) identifying a modulator compound based on a decrease or increase in binding between the neuropilin polypeptide and the VEGF-C polypeptide in the presence of the putative modulator compound, as compared to binding in the absence of the putative modulator compound.

In one variation, the method further includes a step (d) of making a modulator composition by formulating a modulator identified according to step (c) in a carrier, preferably a pharmaceutically acceptable carrier. A modulator so formulated is useful in animal studies and also as a therapeutic for administration to image tissues or treat diseases associated with neuropilin- VEGF-C interactions, wherein the administration of a compound could interfere with detrimental activity of these molecules, or promote beneficial activity. Thus, in still another variation, the method further includes a step (e) of administering the modulator composition to an animal that comprises cells that express the neuropilin receptor, and determining physiological effects of the modulator composition in the animal. The animal may be human, or any animal model for human medical research, or an animal of importance as livestock or pets. In a preferred variation, the animal (including humans) has a disease or condition characterized by aberrant neuropilin-2/VEGF-C biology, and the

modulator improves the animal's state (e.g., by reducing disease symptoms, slowing disease progression, curing the disease, or otherwise improving clinical outcome).

Step (a) of the foregoing methods involves contacting a neuropilin composition with a VEGF-C composition in the presence and absence of a compound.

- 5 By "neuropilin composition" is meant any composition that includes a whole neuropilin receptor polypeptide, or includes at least the portion of the neuropilin polypeptide needed for the particular assay - in this case the portion of the neuropilin polypeptide involved in VEGF-C binding. Exemplary neuropilin compositions include: (i) a composition comprising a purified polypeptide that comprises an entire  
10 neuropilin protein or that comprises a neuropilin receptor extracellular domain fragment that binds VEGF-C polypeptides; (ii) a composition containing phospholipid membranes that contain neuropilin receptor polypeptides on their surface; (iii) a living cell recombinantly modified to express increased amounts of a neuropilin receptor polypeptide on its surface (e.g., by inserting a neuropilin gene, preferably with an  
15 attached promoter, into a cell; or by amplifying an endogenous neuropilin gene; or by inserting an exogenous promoter or other regulatory sequence to up-regulate an endogenous neuropilin gene); and (iv) any isolated cell or tissue that naturally expresses the neuropilin receptor polypeptide on its surface. For certain assay formats, it may be desirable to bind the neuropilin molecule of interest (e.g., a  
20 composition comprising a polypeptide comprising a neuropilin receptor extracellular domain fragment) to a solid support such as a bead or assay plate well. "Neuropilin composition" is intended to include such structures as well. Likewise, fusion proteins are contemplated wherein the neuropilin polypeptide is fused to another protein (such as an antibody Fc fragment) to improve solubility, or to provide a marker epitope, or  
25 serve any other purpose. For other assay formats, soluble neuropilin peptides may be preferred. In one preferred variation, the neuropilin composition comprises a polypeptide comprising a neuropilin receptor extracellular domain fragment fused to an immunoglobulin Fc fragment. Although two family members are currently known, neuropilin-1 and neuropilin-2, practice of the invention with other neuropilin receptor  
30 family members that are subsequently discovered is contemplated. The neuropilin receptor chosen is preferably of vertebrate origin, more preferably mammalian, still more preferably primate, and still more preferably human. And, while it will be apparent that the assay will likely give its best results if the functional portion of the

chosen neuropilin receptor is identical in amino acid sequence to the native receptor, it will be apparent that the invention can still be practiced if variations have been introduced in the neuropilin sequence that do not eliminate its VEGF-C binding properties. Use of variant sequences with at least 90%, 95%, 96%, 97%, 98%, or  
5 99% amino acid identity is specifically contemplated.

VEGF-C molecules occur naturally as secreted factors that undergo several enzymatic cleavage reactions before release into the surrounding milieu. Thus, "VEGF-C composition" means any composition that includes a prepro-VEGF-C polypeptide, the intermediate and final cleavage products of prepro-VEGF-C,  
10  $\Delta$ NACVEGF-C, or includes at least the portion of the VEGF-C needed for the particular assay - in this case the portion involved in binding to a neuropilin receptor. Exemplary VEGF-C compositions include: (i) a composition comprising purified complete prepro-VEGF-C polypeptide or comprising a prepro-VEGF-C polypeptide fragment that binds the neuropilin receptor chosen for the assay; and (ii) conditioned  
15 media from a cell that secretes the VEGF-C protein. For certain assay formats, it may be desirable to bind the VEGF-C molecule of interest (e.g., a polypeptide comprising VEGF-C fragment) to a solid support such as a bead or assay plate well. "VEGF-C composition" is intended to include such structures as well. Likewise, fusion proteins are contemplated. The data provided herein establishes that isoforms of VEGF-C  
20 bind both neuropilin-1 and neuropilin-2. The VEGF-C polypeptide chosen is preferably of vertebrate origin, more preferably mammalian, still more preferably primate, and still more preferably human. In one embodiment the VEGF-C composition comprises a fragment of human prepro-VEGF-C that contains amino acids 103-227 of SEQ. ID NO.: 24. In another embodiment, the VEGF-C  
25 composition comprises amino acids 32-227 of the human prepro-VEGF-C sequence of SEQ. ID NO.: 24. While it will be apparent that the assay will likely give its best results if the functional portion of the chosen VEGF-C is identical in amino acid sequence to the corresponding portion of the native VEGF-C, it will be apparent that the invention can still be practiced if variations have been introduced in the VEGF-C  
30 sequence that do not eliminate its neuropilin receptor binding properties. Use of variant sequences with at least 90%, 95%, 96%, 97%, 98%, or 99% amino acid identity is specifically contemplated.

The putative modulator compound that is employed in step (a) can be any organic or inorganic chemical or biological molecule or composition of matter that one would want to test for ability to modulate neuropilin-VEGF-C interactions. Since the most preferred modulators will be those that can be administered as  
5 therapeutics, it will be apparent that molecules with limited toxicity are preferred. However, toxicity can be screened in subsequent assays, and can be "designed out" of compounds by pharmaceutical chemists. Screening of chemical libraries such as those customarily kept by pharmaceutical companies, or combinatorial libraries, peptide libraries, and the like is specifically contemplated.

10 Step (b) of the above-described method includes detecting binding between neuropilin and VEGF-C in the presence and absence of the compound. Any technique for detecting intermolecular binding may be employed. Techniques that provide quantitative measurements of binding are preferred. For example, one or both of neuropilin/VEGF-C may comprise a label, such as a radioisotope, a fluorophore, a  
15 fluorescing protein (e.g., natural or synthetic green fluorescent proteins), a dye, an enzyme or substrate, or the like. Such labels facilitate quantitative detection with standard laboratory machinery and techniques. Immunoassays represent a common and highly effective body of techniques for detecting binding between two molecules.

When the neuropilin composition comprises a cell that expresses  
20 neuropilin naturally or recombinantly on its surface, it will often be possible to detect VEGF-C binding indirectly, e.g., by detecting or measuring a VEGF-C binding-induced physiological change in the cell. Such possible changes include phosphorylation of the neuropilin associated VEGF-receptor; cell chemotaxis; cell growth; DNA synthesis; changes in cellular morphology; ionic fluxes; or the like.

25 Step (c) of the outlined method involves identifying a modulator compound on the basis of increased or decreased binding between the neuropilin receptor polypeptide and the VEGF-C polypeptide in the presence of the putative modulator compound as compared to such binding in the absence of the putative modulator compound. Generally, more attractive modulators are those that will  
30 activate or inhibit neuropilin-VEGF-C binding at low concentrations, thereby permitting use of the modulators in a pharmaceutical composition at lower effective doses.

As described below in greater detail, the growth factor VEGF-D shares amino acid sequence similarity to VEGF-C, and is known to undergo similar proteolytic processing from a prepro-VEGF-D form into smaller, secreted growth factor forms, and is known to share two VEGFR receptors with VEGF-C, namely, VEGFR-3 and VEGFR-2. Due to these and other similarities, it is expected that VEGF-D binds neuropilins in a manner analogous to what has been shown with VEGF-C, and such binding may be confirmed with assays described in the examples (by substituting VEGF-D). Accordingly, as another aspect of the invention, practice of the above-described screening method (and other methods described in the ensuing paragraphs) is contemplated wherein VEGF-D polypeptides are employed in lieu of VEGF-C polypeptides. A detailed description of the human VEGF-D gene and protein are provided in Achen, et al., Proc. Nat'l Acad. Sci. U.S.A., 95(2): 548-553 (1998); International Patent Publication No. WO 98/07832, published 26 February 1998; and in Genbank Accession No. AJ000185, all incorporated herein by reference.

In another embodiment, the invention provides a method for screening for selectivity of a modulator of VEGF-C biological activity. The term "selectivity" - when used herein to describe modulators - refers to the ability of a modulator to modulate one protein-protein interaction (e.g., VEGF-C binding with neuropilin-2) with minimal effects on the interaction of another protein-protein interaction of one or more of the binding pairs (e.g., VEGF-C binding with VEGFR-2, or VEGFR-3, or neuropilin-1). More selective modulators significantly alter the first protein-protein interaction with minimal effects on the other protein-protein interaction, whereas non-selective modulators will alter two or more protein-protein interactions. It will be appreciated that selectivity is of immense interest to the design of effective pharmaceuticals. For example, in some circumstances, it may be desirable to identify modulators that alter VEGF-C/neuropilin interactions but not semaphorin/neuropilin interactions, because one wishes to modulate vessel growth but not neurological growth. It may be desirable in some circumstances to non-selectively inhibit all VEGF-C related activities, e.g., in anti-tumor therapy. The molecular interactions identified herein permit novel screening assays to help identify the selectivity of modulators.

For example, VEGF-C molecules are also known ligands for the VEGFR-2 and VEGFR-3 tyrosine kinase receptors. VEGF-C/VEGFR-3 interactions

appear to be integrally involved in the development and maintenance of lymphatic vasculature and may also be involved in cancer metastasis through the lymphatic system. In one instance it may be beneficial to modulate VEGF-C/neuropilin interactions specifically while in another instance it may be useful to selectively  
5 modulate the VEGF-C/VEGFR interactions. The present invention provides counterscreen assays that identify the selectivity of a modulator for neuropilin-VEGF-C binding or VEGF-C-VEGFR binding.

Thus, in one variation, the invention provides a method, comprising steps of:

10 a) contacting a VEGF-C composition with a neuropilin composition in the presence and in the absence of a compound and detecting binding between the VEGF-C and the neuropilin (in the compositions) in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the VEGF-C and the  
15 neuropilin;

b) contacting a VEGF-C composition with a composition comprising a VEGF-C binding partner in the presence and in the absence of the compound and detecting binding between the VEGF-C and the binding partner in the presence and absence of the compound, wherein differential binding in the presence and absence of  
20 the compound identifies the compound as a modulator of binding between the VEGF-C and the binding partner; and wherein the binding partner is selected from the group consisting of:

(i) a polypeptide comprising a VEGFR-3 extracellular domain;  
and

25 (ii) a polypeptide comprising a VEGFR-2 extracellular domain;  
and

(c) identifying the selectivity of the modulator compound in view of the binding detected in steps (a) and (b).

Step (a) of the above embodiment involves contacting a neuropilin  
30 composition with a VEGF-C composition as described previously. Step (b) of the outlined method involves contacting a VEGF-C composition as described in step (a) with a composition comprising a VEGF-C binding partner in the presence and in the



absence of the same compound. The VEGF-C binding partner is selected from the group consisting of: (i) a polypeptide comprising a VEGFR-3 extracellular domain; and (ii) a polypeptide comprising a VEGFR-2 extracellular domain. Thus, the above-described embodiment involves measuring selectivity of a modulator of VEGF-C/neuropilin binding in relation to VEGF-C binding to its receptors, VEGFR-2 and VEGFR-3. The VEGF-C binding partner chosen is preferably of vertebrate origin, more preferably mammalian, still more preferably primate, and still more preferably human. And, while it will be apparent that the assay will likely give its best results if the functional portion of the chosen VEGF-C binding partner is identical in amino acid sequence to the native VEGF-C binding partner, it will be apparent that the invention can still be practiced if variations have been introduced in the VEGF-C binding partner sequence that do not eliminate its VEGF-C binding properties. Use of variant sequences with at least 90%, 95%, 96%, 97%, 98%, or 99% amino acid identity is specifically contemplated. Any technique for detecting intermolecular binding may be employed. For example, one or both of the binding partner or the VEGF-C may comprise a label, such as a radioisotope, a fluorophore, a fluorescing protein (e.g., natural or synthetic green fluorescent proteins), a dye, an enzyme or substrate, or the like. Such labels facilitate detection with standard laboratory machinery and techniques.

In one variation, the binding partner composition comprises a cell that expresses the binding partner naturally or recombinantly on its surface. In this situation, it will often be possible to detect VEGF-C binding indirectly, e.g., by detecting or measuring a VEGF-C binding-induced physiological change in the cell. Such possible changes include phosphorylation of the associated VEGFR; cell chemotaxis; cell growth, changes in cellular morphology; ionic fluxes, or the like.

Step (c) of the outlined method involves identifying the selectivity of the modulator compound on the basis of increased or decreased binding in steps (a) and (b). A compound that is a selective modulator causes significant differential binding in either step (a) or step (b), but does not cause significant differential binding in both steps (a) and (b). A non-specific modulator causes significant differential binding in both steps (a) and (b).

In still another embodiment, the invention provides a method for screening for selectivity of a modulator of neuropilin biological activity, comprising steps of:

- a) contacting a neuropilin composition with a VEGF-C composition in the presence and in the absence of a compound and detecting binding between the neuropilin and the VEGF-C in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the neuropilin and the VEGF-C;
- b) contacting a neuropilin composition with a composition comprising a neuropilin binding partner in the presence and in the absence of the compound and detecting binding between the neuropilin and the binding partner in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the neuropilin and the binding partner; and wherein the binding partner is selected from the group consisting of:
  - (i) a polypeptide comprising an amino acid sequence of a semaphorin 3 polypeptide,
  - (ii) a polypeptide comprising a VEGF-A amino acid sequence, a VEGF-B amino acid sequence, a VEGF-D amino acid sequence, a PlGF-2 amino acid sequence, a VEGFR-1 amino acid sequence, a VEGFR-2 amino acid sequence, a VEGFR-3 amino acid sequence; and
  - (iii) a polypeptide comprising an amino acid sequence of a plexin polypeptide
- d) identifying the selectivity of the modulator compound in view of the binding detected in steps (a) and (b).

Step (a) of the above embodiment involves contacting a neuropilin composition with a VEGF-C composition as described previously. Step (b) of the outlined method involves contacting a neuropilin composition as described in step (a) with a composition comprising a neuropilin binding partner in the presence and in the absence of a compound. The neuropilin binding partner comprises any protein other than VEGF-C that the neuropilin binds. Exemplary binding partners include the following polypeptides: a polypeptide comprising the amino acid sequence of a

semaphorin 3 family member polypeptide; a polypeptide comprising a VEGF-A amino acid sequence, a polypeptide comprising a VEGF-B amino acid sequence, a polypeptide comprising a VEGF-D amino acid sequence, a polypeptide comprising a PlGF-2 amino acid sequence, a polypeptide comprising a VEGFR-1 amino acid sequence, a polypeptide comprising a VEGFR-2 amino acid sequence, a polypeptide comprising a VEGFR-3 amino acid sequence; and a polypeptide comprising the amino acid sequence of a plexin family member. The binding partners chosen are preferably of vertebrate origin, more preferably mammalian, still more preferably primate, and still more preferably human. And, while it will be apparent that the assay will likely give its best results if the functional portion of the chosen neuropilin binding partner is identical in amino acid sequence to the native sequence, it will be apparent that the invention can still be practiced if variations have been introduced in the native sequence that do not eliminate its neuropilin binding properties. Use of variant sequences with at least 90%, 95%, 96%, 97%, 98%, or 99% amino acid identity is specifically contemplated.

The above-described method includes detecting binding between the neuropilin composition and the binding partner in the presence and absence of the compound. Any technique for detecting intermolecular binding may be employed. For example, one or both of the binding partner or the neuropilin may comprise a label, such as a radioisotope, a fluorophore, a fluorescing protein (e.g., natural or synthetic green fluorescent proteins), a dye, an enzyme or substrate, or the like. Such labels facilitate detection with standard laboratory machinery and techniques.

Step (c) of the outlined method involves identifying the selectivity of the modulator compound on the basis of increased or decreased binding in steps (a) and (b), and having the characteristics of a selective modulator compound as described previously.

In an additional embodiment, the invention provides a method of screening for modulators of binding between a neuropilin growth factor receptor and a VEGFR-3 polypeptide comprising steps of:

a) contacting a neuropilin composition with a VEGFR-3 composition in the presence and in the absence of a putative modulator compound;

b) detecting binding between the neuropilin and the VEGFR-3 in the presence and absence of the putative modulator compound; and

c) identifying a modulator compound based on a decrease or increase in binding between the neuropilin composition and the VEGFR-3 composition in the presence of the putative modulator compound, as compared to binding in the absence of the putative modulator compound.

Step (a) of the aforementioned method involves contacting a neuropilin composition as described with a VEGFR-3 composition in the presence and absence of a putative modulator compound. The neuropilin composition contemplated is described previously. A VEGFR-3 composition comprises a member selected from the group consisting of (i) a composition comprising a purified polypeptide that comprises an entire VEGFR-3 protein or that comprises a VEGFR-3 fragment that binds the neuropilin; (ii) a composition containing phospholipid membranes that contain VEGFR-3 polypeptides on their surface; (iii) a living cell recombinantly modified to express increased amounts of a VEGFR-3 on its surface; and (iv) any isolated cell or tissue that naturally expresses the VEGFR-3 on its surface. For certain assay formats, it may be desirable to bind the VEGFR-3 molecule of interest (e.g., a polypeptide comprising a VEGFR-3 extracellular domain fragment) to a solid support such as a bead or assay plate well. "VEGFR-3 composition" is intended to include such structures as well. Likewise, fusion proteins are contemplated. For other assay formats, soluble VEGFR-3 peptides may be preferred. In one preferred variation, the VEGFR-3 receptor composition comprises a VEGFR-3 receptor fragment fused to an immunoglobulin Fc fragment.

Step (b) of the above method involves detecting binding between the neuropilin composition and the VEGFR-3 composition in the presence and absence of the compound. Any technique for detecting intermolecular binding may be employed. For example, one or both of neuropilin/VEGFR-3 may comprise a label, such as a radioisotope, a fluorophore, a fluorescing protein (e.g., natural or synthetic green fluorescent proteins), a dye, an enzyme or substrate, or the like. Such labels facilitate detection with standard laboratory machinery and techniques.

Generally, more attractive modulators are those that will activate or inhibit neuropilin-VEGFR-3 binding at lower concentrations, thereby permitting use of the modulators in a pharmaceutical composition at lower effective doses.

In another embodiment, the invention provides for a method for  
5 screening for selectivity of a modulator of VEGFR-3 biological activity, comprising steps of:

a) contacting a VEGFR-3 composition with a neuropilin composition in the presence and in the absence of a compound and detecting binding between the VEGFR-3 and the neuropilin in the presence and absence of the compound, wherein  
10 differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the VEGFR-3 and the neuropilin;

b) contacting a VEGFR-3 composition with a composition comprising a VEGFR-3 binding partner in the presence and in the absence of a compound and detecting binding between the VEGFR-3 and the binding partner in the presence and  
15 absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the VEGFR-3 and the binding partner; and wherein the binding partner is selected from the group consisting of:

(i) a polypeptide comprising a VEGF-C polypeptide; and  
20 (ii) a polypeptide comprising a VEGF-D polypeptide; and

c) identifying the selectivity of the modulator compound in view of the binding detected in steps (a) and (b).

A selective modulator causes significant differential binding in either step (a) or step (b), but does not cause significant differential binding in both steps (a)  
25 and (b).

It will be apparent that the foregoing selectivity screens represent only a portion of the specific selectivity screens of the present invention, because the neuropilins, VEGF-C, VEGF-D, and VEGFR-3 all have multiple binding partners, creating a number of permutations for selectivity screens. Any selectivity screen that  
30 involves looking at one of the following interactions: (i) neuropilin-1/VEGF-C; (ii) neuropilin-1/VEGF-D; (iii) neuropilin-2/VEGF-C; (iv) neuropilin-2/VEGF-D; (v)

neuropilin-1/VEGFR-3; and (vi) neuropilin-2/VEGFR3; together with at least one other interaction (e.g., a known interaction of one of these molecules, or a second interaction from the foregoing list) is specifically contemplated as part of the present invention.

5               Likewise, all of the screens for modulators and the selectivity screens optionally comprising one or both of the following steps: (1) making a modulator composition by formulating a chosen modulator in a pharmaceutically acceptable carrier; and (2) administering the modulator so formulated to an animal or human and determining the effect of the modulator. Preferably, the animal or human has a  
10           disease or condition involving one of the foregoing molecular interactions, and the animal or human is monitored to determine the effect of the modulator on the disease or condition, which, hopefully, is ameliorated or cured.

                  The discovery of neuropilin-2 and neuropilin-1 binding to VEGF-C molecules provides new and useful materials and methods for investigating biological  
15           processes involved in many currently known disease states. For example, the invention provides for a method of modulating growth, migration, or proliferation of cells in a mammalian organism, comprising a step of:

                  (a) identifying a mammalian organism having cells that express a neuropilin receptor; and

20           (b) administering to said mammalian organism a composition, said composition comprising a neuropilin polypeptide or fragment thereof that binds to a VEGF-C polypeptide;

                  wherein the composition is administered in an amount effective to modulate growth, migration, or proliferation of cells that express neuropilin in the  
25           mammalian organism. Administration of soluble forms of the neuropilin is preferred.

                  Preferably, the mammalian organism is human. Also, the cells preferably comprise vascular endothelial cells, especially cells of lymphatic origin, such as human microvascular endothelial cells (HMVEC) and human cutaneous fat pad microvascular cells (HUVEC). In a highly preferred embodiment, the organism  
30           has a disease characterized by aberrant growth, migration, or proliferation of endothelial cells. The administration of the agent beneficially alters the aberrant

growth, migration, or proliferation, e.g., by correcting it, or reducing its severity, or reducing its deleterious symptoms or effects.

For example, in one variation, the animal has a cancer, especially a cancerous tumor characterized by vasculature containing neuropilin-expressing endothelial cells. A composition is selected that will decrease growth, migration, or proliferation of the cells, and thereby retard the growth of the tumor by preventing growth of new vasculature. In such circumstances, one may wish to administer agents that inhibit other endothelial growth factor/receptor interactions, such as inhibitors of the VEGF-family of ligands; endostatins; inhibitory angiopoietins, or the like. Exemplary inhibitors include antibody substances specific for the growth factors or their ligands. The invention further contemplates treating lymphangioamas, lymphangiosarcomas, and metastatic tumors, which exhibit VEGFR-3 expressing vascular endothelial cells or VEGFR-3 expressing lymphatic endothelial cells. In one embodiment, administration of a composition that inhibits the interaction of VEGFR-3 with its ligand diminishes or abolishes lymphangiogenesis and retards the spread of cancerous cells. In an additional embodiment, administration of a composition that stimulates the interaction of VEGFR-3 with its ligand enhances lymphangiogenesis and speeds wound healing.

Further contemplated is a method of modulating growth, migration, or proliferation of cells in a mammalian organism, comprising steps of:

(a) identifying a mammalian organism having cells that express a neuropilin receptor; and

(b) administering to said mammalian organism a composition, said composition comprising a bispecific antibody specific for the neuropilin receptor and for a VEGF-C polypeptide, wherein the composition is administered in an amount effective to modulate growth, migration, or proliferation of cells that express the neuropilin receptor in the mammalian organism. In an alternative embodiment, the bispecific antibody is specific for the neuropilin receptor and for a VEGFR-3 polypeptide.

In one embodiment, the invention provides a bispecific antibody which specifically binds a neuropilin receptor and a VEGF-C polypeptide. Alternatively, the

invention provides a bispecific antibody which specifically binds to the neuropilin receptor and a VEGFR-3 polypeptide.

In another embodiment, the invention can also be used to inhibit neural degeneration in the central nervous system. Development of scars surrounding neuronal injury in either the peripheral and more specifically the central nervous system has been associated with constitutive expression of the semaphorin ligands. Also, upregulation of Sema3F, a primary ligand for the neuropilin-2 receptor, has been detected in the brains of Alzheimer's patients. The present invention provides for a means to alter the semaphorin-neuropilin interactions using VEGF-C compositions that specifically interfere with semaphorin activity in the nervous system.

For example, the invention provides for a method of modulating aberrant growth, or neuronal scarring in a mammalian organism, comprising a step of:

- (a) identifying a mammalian organism having neuronal cells that express a neuropilin receptor; and
- (b) administering to said mammalian organism a composition, said composition comprising a VEGF-C polypeptide or fragment thereof that binds to the neuropilin receptor;

wherein the composition is administered in an amount effective to reduce neuronal scarring in cells that express neuropilin in the mammalian organism.

Other conditions to treat include inflammatory diseases (e.g., Rheumatoid arthritis, chronic wounds and atherosclerosis).

Similarly, the invention provides a polypeptide comprising a fragment of VEGF-C that binds to a neuropilin receptor, for use in the manufacture of a medicament for the treatment of diseases characterized by aberrant growth, migration, or proliferation of cells that express a neuropilin receptor.

Likewise, the invention provides a polypeptide comprising a fragment of a neuropilin that binds to a VEGF-C, for use in the manufacture of a medicament for the treatment of diseases characterized by aberrant growth, migration, or proliferation of cells that express a neuropilin receptor. Soluble forms of the neuropilin, lacking the transmembrane domain, are preferred. The invention also



provides for a polypeptide comprising a fragment of a neuropilin receptor that binds to a VEGFR-3 polypeptide, for use in the manufacture of a medicament for the treatment of diseases characterized by aberrant growth, migration, or proliferation of cells that express a VEGFR-3 polypeptide.

5                   With respect to aspects of the invention that involve administration of protein agents to mammals, a related aspect of the invention comprises gene therapy whereby a gene encoding the protein of interest is administered in a manner to effect expression of the protein of interest in the animal. For example, the gene of interest is attached to a suitable promoter to promote expression of the protein in the target cell  
10 of interest, and is delivered in any gene therapy vector capable of delivering the gene to the cell, including adenovirus vectors, adeno-associated virus vectors, liposomes, naked DNA transfer, and others.

                  Additional features and variations of the invention will be apparent to those skilled in the art from the entirety of this application, and all such features are  
15 intended as aspects of the invention.

                  Likewise, features of the invention described herein can be re-combined into additional embodiments that also are intended as aspects of the invention, irrespective of whether the combination of features is specifically mentioned above as an aspect or embodiment of the invention. Also, only such  
20 limitations which are described herein as critical to the invention should be viewed as such; variations of the invention lacking limitations which have not been described herein as critical are intended as aspects of the invention.

                  In addition to the foregoing, the invention includes, as an additional aspect, all embodiments of the invention narrower in scope in any way than the variations specifically mentioned above. Although the applicant(s) invented the full  
25 scope of the claims appended hereto, the claims appended hereto are not intended to encompass within their scope the prior art work of others. Therefore, in the event that statutory prior art within the scope of a claim is brought to the attention of the applicants by a Patent Office or other entity or individual, the applicant(s) reserve the  
30 right to exercise amendment rights under applicable patent laws to redefine the subject matter of such a claim to specifically exclude such statutory prior art or obvious variations of statutory prior art from the scope of such a claim. Variations of

the invention defined by such amended claims also are intended as aspects of the invention.

### BRIEF DESCRIPTION OF THE DRAWINGS

- 5                    Figure 1 depicts the construction of the neuropilin-2 IgG fusion protein a17 and a22 expression vectors.

### DETAILED DESCRIPTION OF THE INVENTION

- The present invention is based, in part, on the discovery of novel  
 10    interaction between proteins that have previously been characterized in the literature, but whose interactions were not previously appreciated. A number of the molecules are explicitly set forth with annotations to the Genbank database or to a Sequence Listing appended hereto, but it will be appreciated that sequences for species  
 15    homologous ("orthologs") are also easily retrieved from databases and/or isolated from natural sources. Thus, the following table and description should be considered exemplary and not limiting.

#### A. Molecules of interest to the present invention.\*

<u>Molecule</u>	<u>Genbank Accession #</u>	<u>SEQ ID NO.</u>
Neuropilin-1	NM003873	1 and 2
Soluble Neuropilin-1, s11	AF280547	
Neuropilin-2 [a(17)]	NM003872	3 and 4
a(0)	AF022859	
a(17)	AF022860	
b(0)	AF280544	
b(5)	AF280545	
Soluble Neuropilin-2, s9	AF280546	
Murine neuropilin-1	D50086	5 and 6

<u>Molecule</u>	<u>Genbank Accession #</u>	<u>SEQ ID NO.</u>
Murine neuropilin-2		
a(0)	AF022854	
a(5)	AF022861	
a(17)	AF022855	7 and 8
a(22)	AF022856	
b(0)	AF022857	
b(5)	AF022858	
Semaphorin 3A	NM006080	9 and 10
Semaphorin 3B	NM004636	11 and 12
Semaphorin 3C	NM006379	13 and 14
Semaphorin 3E	NM012431	15 and 16
Semaphorin 3F	NM004186	17 and 18
VEGF-A	Q16889	19 and 20
VEGF165	M32977	
VEGF-B	U48801	21 and 22
VEGF-C	X94216	23 and 24
VEGF-D	AJ000185	25 and 26
VEGF-E	S67522	
PlGF	NM002632	27 and 28
VEGFR-1	X51602	
VEGFR-2	L04947	29 and 30
VEGFR-3	X68203	31 and 32
Plexin-A1	X87832	
Plexin-A2	NM025179	

<u>Molecule</u>	<u>Genbank Accession #</u>	<u>SEQ ID NO.</u>
PDGF-A,-B,-C	NM002607; NM002608; NM016205	
PDGFR-A,-B	NM006206; NM002609	

\* All Sequences of Human origin unless otherwise noted.

### *The Neuropilin Family*

The neuropilin-1 and neuropilin-2 genes span over 120 and 112 kb, respectively, and are comprised of 17 exons, five of which are identical in size in both genes, suggesting genetic duplication of these genes (Rossignol et al, Genomics 70:211-22. 2000). Several splice variants of the neuropilins have been isolated to date, the functional significance of which is currently under investigation.

Isoforms of NRP-2, designated NRP2a and NRP2b, were first isolated from the mouse genome (Chen et al, Neuron 19:547-59. 1997). In mouse, NRP2a isoforms contain insertions of 0, 5, 17, or 22 (5 + 17) amino acids after amino acid 809 of NRP-2 and are named NRP2a(0) (Genbank Accession No. AF022854)(SEQ ID NO. 7 and 8), NRP2a(5) (Genbank Accession No. AF022861), NRP2a(17) (Genbank Accession No. AF022855), and NRP2a(22)(Genbank Accession No. AF022856), respectively. Only two human NRP2a isoforms homologous to the mouse variants NRP2a(17) (Genbank Accession No. AF022860) (SEQ ID NO. 3 and 4) and NRP2a(22), have been elucidated. The human a(22) isoform contains a five amino acid insertion, sequence GENFK, after amino acid 808 in NRP2a(17). Tissue analysis of brain, heart, lung, kidney liver and placenta shows that the a(17) isoform is more abundant in all of these sites.

The human NRP2b isoforms appear to express an additional exon, designated exon 16b, not present in either NRP2a or NRP-1. Two human NRP2b isoforms homologous to mouse NRP2b(0) (Genbank Accession No. AF022857) and NRP2b(5) (Genbank Accession No. AF022858) have been identified which contain either a 0 or 5 amino acid insert (GENFK) after amino acid 808 in NRP2b(0) (Rossignol et al., Genomics 70:211-22. 2000). Tissue distribution analysis demonstrates a higher expression of human NRP2b(0) (Genbank Accession No. AF280544) over NRP2b(5) (Genbank Accession No. AF280545) in adult brain, heart,

lung, kidney, liver, and placenta. The NRP2a and NRP2b isoforms demonstrate divergence in their C terminal end, after amino acid 808 of NRP2 which is in the linker region between the c domain and the transmembrane domain. This differential splicing may lead to the difference seen in tissue expression of the two isoforms, where NRP2a is expressed more abundantly in the placenta, liver, and lung with only detectable levels of NRP2b, while NRP2b is found in skeletal muscle where NRP2a expression is low. Both isoforms are expressed in heart and small intestine.

In addition to genetic isoforms of the neuropilins, truncated soluble forms of the proteins have also been cloned (Gagnon et al, Proc. Natl. Acad. Sci USA 97:2573-78 2000; Rossignol et al, Genomics 70:211-22. 2000). Naturally occurring truncated forms of the NRP-1 protein, s11NRP1 (Genbank Accession No. AF280547) and s12NRP1, have been cloned, that encode 704 and 644 amino acid neuropilin-1, respectively, and contain the a and b domains but not the c domain. The s12NRP1 variant is generated by pre-mRNA processing in intron 12. The s11NRP1 truncation occurs after amino acid 621 and lacks the 20 amino acids encoded by exon 12, but contains coding sequence found within intron 11 that gives it 83 novel amino acids at the C-terminus. This intron derived sequence does not contain any homology to known proteins.

A natural, soluble form of NRP-2 has also been identified which encodes a 555 amino acid protein containing the a domains, b1 domain, and part of the b2 domain, lacking the last 48 amino acids of this region. The truncation occurs after amino acid 547 within intron 9, thus the protein has been named s9NRP2 (Genbank Accession No. AF2805446), and adds 8 novel amino acids derived from the intron cleavage (VGCSVWRPL) at the C-terminus. Gagnon et al (Proc. Natl. Acad. Sci USA 97:2573-78. 2000) report that soluble neuropilin-1 isoform s12NRP1 is capable of binding VEGF165 equivalent to the full length protein, but acts as an antagonist of VEGF165 binding, inhibiting VEGF165 activity and showing anti-tumor properties in a rat prostate carcinoma model.

#### *The PDGF/VEGF Family*

The PDGF/VEGF family of growth factors includes at least the following members: PDGF-A (see e.g., GenBank Acc. No. X06374), PDGF-B (see e.g., GenBank Acc. No. M12783), VEGF (see e.g., GenBank Acc. No. Q16889 referred to herein for clarity as VEGF-A or by particular isoform), PlGF (see e.g.,

GenBank Acc. No. X54936 placental growth factor), VEGF-B (see e.g., GenBank Acc. No. U48801; also known as VEGF-related factor (VRF)), VEGF-C (see e.g., GenBank Acc. No. X94216; also known as VEGF related protein (VRP or VEGF-2)), VEGF-D (also known as c-fos-induced growth factor (FIGF); see e.g., Genbank Acc. No. AJ000185), VEGF-E (also known as NZ7 VEGF or OV NZ7; see e.g., GenBank Acc. No. S67522), NZ2 VEGF (also known as OV NZ2; see e.g., GenBank Acc. No. S67520), D1701 VEGF-like protein (see e.g., GenBank Acc. No. AF106020; Meyer et al., EMBO J 18:363-374), and NZ10 VEGF-like protein (described in International Patent Application PCT/US99/25869) [Stacker and Achen, Growth Factors 17:1-11 (1999); Neufeld et al., FASEB J 13:9-22 (1999); Ferrara, J Mol Med 77:527-543 (1999)]. The PDGF/VEGF family proteins are predominantly secreted glycoproteins that form either disulfide-linked or non-covalently bound homo- or heterodimers whose subunits are arranged in an anti-parallel manner [Stacker and Achen, Growth Factors 17:1-11 (1999); Muller et al., Structure 5:1325-1338 (1997)].

The VEGF subfamily is composed of PDGF/VEGF members which share a VEGF homology domain (VHD) characterized by the sequence: C-X(22-24)-P-[PSR]-C-V-X(3)-R-C-[GSTA]-G-C-C-X(6)-C-X(32-41)-C.

VEGF-A was originally purified from several sources on the basis of its mitogenic activity toward endothelial cells, and also by its ability to induce microvascular permeability, hence it is also called vascular permeability factor (VPF). VEGF-A has subsequently been shown to induce a number of biological processes including the mobilization of intracellular calcium, the induction of plasminogen activator and plasminogen activator inhibitor-1 synthesis, promotion of monocyte migration in vitro, induction of antiapoptotic protein expression in human endothelial cells, induction of fenestrations in endothelial cells, promotion of cell adhesion molecule expression in endothelial cells and induction of nitric oxide mediated vasodilation and hypotension [Ferrara, J Mol Med 77: 527-543 (1999); Neufeld et al., FASEB J 13: 9-22 (1999); Zachary, Intl J Biochem Cell Bio 30: 1169-1174 (1998)].

VEGF-A is a secreted, disulfide-linked homodimeric glycoprotein composed of 23 kD subunits. Five human VEGF-A isoforms of 121, 145, 165, 189 or 206 amino acids in length (VEGF<sub>121-206</sub>), encoded by distinct mRNA splice variants, have been described, all of which are capable of stimulating mitogenesis in endothelial cells. However, each isoform differs in biological activity, receptor

specificity, and affinity for cell surface- and extracellular matrix-associated heparan-sulfate proteoglycans, which behave as low affinity receptors for VEGF-A. VEGF<sub>121</sub> does not bind to either heparin or heparan-sulfate; VEGF<sub>145</sub> and VEGF<sub>165</sub> (GenBank Acc. No. M32977) are both capable of binding to heparin; and VEGF<sub>189</sub> and VEGF<sub>206</sub> show the strongest affinity for heparin and heparan-sulfates. VEGF<sub>121</sub>, VEGF<sub>145</sub>, and VEGF<sub>165</sub> are secreted in a soluble form, although most of VEGF<sub>165</sub> is confined to cell surface and extracellular matrix proteoglycans, whereas VEGF<sub>189</sub> and VEGF<sub>206</sub> remain associated with extracellular matrix. Both VEGF<sub>189</sub> and VEGF<sub>206</sub> can be released by treatment with heparin or heparinase, indicating that these isoforms are bound to extracellular matrix via proteoglycans. Cell-bound VEGF<sub>189</sub> can also be cleaved by proteases such as plasmin, resulting in release of an active soluble VEGF<sub>110</sub>. Most tissues that express VEGF are observed to express several VEGF isoforms simultaneously, although VEGF<sub>121</sub> and VEGF<sub>165</sub> are the predominant forms, whereas VEGF<sub>206</sub> is rarely detected [Ferrara, J Mol Med 77:527-543 (1999)]. VEGF<sub>145</sub> differs in that it is primarily expressed in cells derived from reproductive organs [Neufeld et al., FASEB J 13:9-22 (1999)].

The pattern of VEGF-A expression suggests its involvement in the development and maintenance of the normal vascular system, and in angiogenesis associated with tumor growth and other pathological conditions such as rheumatoid arthritis. VEGF-A is expressed in embryonic tissues associated with the developing vascular system, and is secreted by numerous tumor cell lines. Analysis of mice in which VEGF-A was knocked out by targeted gene disruption indicate that VEGF-A is critical for survival, and that the development of the cardiovascular system is highly sensitive to VEGF-A concentration gradients. Mice lacking a single copy of VEGF-A die between day 11 and 12 of gestation. These embryos show impaired growth and several developmental abnormalities including defects in the developing cardiovascular system. VEGF-A is also required post-natally for growth, organ development, regulation of growth plate morphogenesis and endochondral bone formation. The requirement for VEGF-A decreases with age, especially after the fourth postnatal week. In mature animals, VEGF-A is required primarily for active angiogenesis in processes such as wound healing and the development of the corpus luteum. [Neufeld et al., FASEB J 13:9-22 (1999); Ferrara, J Mol Med 77:527-543 (1999)]. VEGF-A expression is influenced primarily by hypoxia and a number of

hormones and cytokines including epidermal growth factor (EGF), TGF- $\beta$ , and various interleukins. Regulation occurs transcriptionally and also post-transcriptionally such as by increased mRNA stability [Ferrara, J Mol Med 77:527-543 (1999)].

5 PIGF, a second member of the VEGF subfamily, is generally a poor stimulator of angiogenesis and endothelial cell proliferation in comparison to VEGF-A, and the in vivo role of PIGF is not well understood. Three isoforms of PIGF produced by alternative mRNA splicing have been described [Hauser et al., Growth Factors 9:259-268 (1993); Maglione et al., Oncogene 8:925-931 (1993)]. PIGF forms  
10 both disulfide-linked homodimers and heterodimers with VEGF-A. The PIGF-VEGF-A heterodimers are more effective at inducing endothelial cell proliferation and angiogenesis than PIGF homodimers. PIGF is primarily expressed in the placenta, and is also co-expressed with VEGF-A during early embryogenesis in the trophoblastic giant cells of the parietal yolk sac [Stacker and Achen, Growth Factors  
15 17:1-11 (1999)].

VEGF-B, described in detail in International Patent Publication No. WO 96/26736 and U.S. Patents 5,840,693 and 5,607,918, incorporated herein by reference, shares approximately 44% amino acid identity with VEGF-A. Although the biological functions of VEGF-B in vivo remain incompletely understood, it has  
20 been shown to have angiogenic properties, and may also be involved in cell adhesion and migration, and in regulating the degradation of extracellular matrix. It is expressed as two isoforms of 167 and 186 amino acid residues generated by alternative splicing. VEGF-B<sub>167</sub> is associated with the cell surface or extracellular matrix via a heparin-binding domain, whereas VEGF-B<sub>186</sub> is secreted. Both VEGF-  
25 B<sub>167</sub> and VEGF-B<sub>186</sub> can form disulfide-linked homodimers or heterodimers with VEGF-A. The association to the cell surface of VEGF<sub>165</sub>-VEGF-B<sub>167</sub> heterodimers appears to be determined by the VEGF-B component, suggesting that heterodimerization may be important for sequestering VEGF-A. VEGF-B is expressed primarily in embryonic and adult cardiac and skeletal muscle tissues  
30 [Joukov et al., J Cell Physiol 173:211-215 (1997); Stacker and Achen, Growth Factors 17:1-11 (1999)]. Mice lacking VEGF-B survive but have smaller hearts, dysfunctional coronary vasculature, and exhibit impaired recovery from cardiac ischemia [Bellomo et al., Circ Res 2000;E29-E35].



A fourth member of the VEGF subfamily, VEGF-C, comprises a VHD that is approximately 30% identical at the amino acid level to VEGF-A. VEGF-C is originally expressed as a larger precursor protein, prepro-VEGF-C, having extensive amino- and carboxy-terminal peptide sequences flanking the VHD, with the C-terminal peptide containing tandemly repeated cysteine residues in a motif typical of Balbiani ring 3 protein. Prepro-VEGF-C undergoes extensive proteolytic maturation involving the successive cleavage of a signal peptide, the C-terminal pro-peptide, and the N-terminal pro-peptide. Secreted VEGF-C protein consists of a non-covalently-linked homodimer, in which each monomer contains the VHD. The intermediate forms of VEGF-C produced by partial proteolytic processing show increasing affinity for the VEGFR-3 receptor, and the mature protein is also able to bind to the VEGFR-2 receptor. [Joukov et al., EMBO J., 16:(13):3898-3911 (1997).] It has also been demonstrated that a mutant VEGF-C, in which a single cysteine at position 156 is either substituted by another amino acid or deleted, loses the ability to bind VEGFR-2 but remains capable of binding and activating VEGFR-3 [U.S. Patent 6,130,071 and International Patent Publication No. WO 98/33917]. In mouse embryos, VEGF-C mRNA is expressed primarily in the allantois, jugular area, and the metanephros. [Joukov et al., J Cell Physiol 173:211-215 (1997)]. VEGF-C is involved in the regulation of lymphatic angiogenesis: when VEGF-C was overexpressed in the skin of transgenic mice, a hyperplastic lymphatic vessel network was observed, suggesting that VEGF-C induces lymphatic growth [Jeltsch et al., Science, 276:1423-1425 (1997)]. Continued expression of VEGF-C in the adult also indicates a role in maintenance of differentiated lymphatic endothelium [Ferrara, J Mol Med 77:527-543 (1999)]. VEGF-C also shows angiogenic properties: it can stimulate migration of bovine capillary endothelial (BCE) cells in collagen and promote growth of human endothelial cells [see, e.g., U.S. Patent 6,245,530; U.S. Patent 6,221,839; and International Patent Publication No. WO 98/33917, incorporated herein by reference].

The prepro-VEGF-C polypeptide is processed in multiple stages to produce a mature and most active VEGF-C polypeptide of about 21-23 kD (as assessed by SDS-PAGE under reducing conditions). Such processing includes cleavage of a signal peptide (SEQ ID NO: 24, residues 1-31); cleavage of a carboxyl-terminal peptide (corresponding approximately to amino acids 228-419 of SEQ ID NO: 24 and having a pattern of spaced cysteine residues reminiscent of a Balbiani

ring 3 protein (BR3P) sequence [Dignam et al., Gene, 88:133-40 (1990); Paulsson et al., J. Mol. Biol., 211:331-49 (1990)] to produce a partially-processed form of about 29 kD; and cleavage (apparently extracellularly) of an amino-terminal peptide (corresponding approximately to amino acids 32-103 of SEQ ID NO: 24) to produced  
5 a fully-processed mature form of about 21-23 kD. Experimental evidence demonstrates that partially-processed forms of VEGF-C (e.g., the 29 kD form) are able to bind the Flt4 (VEGFR-3) receptor, whereas high affinity binding to VEGFR-2 occurs only with the fully processed forms of VEGF-C. It appears that VEGF-C polypeptides naturally associate as non-disulfide linked dimers.

10 Moreover, it has been demonstrated that amino acids 103-227 of SEQ ID NO: 24 are not all critical for maintaining VEGF-C functions. A polypeptide consisting of amino acids 113-213 (and lacking residues 103-112 and 214-227) of SEQ ID NO: 24 retains the ability to bind and stimulate VEGF-C receptors, and it is expected that a polypeptide spanning from about residue 131 to about residue 211 will  
15 retain VEGF-C biological activity. The cysteine residue at position 156 has been shown to be important for VEGFR-2 binding ability. However, VEGF-C  $\Delta$ C156 polypeptides (i.e., analogs that lack this cysteine due to deletion or substitution) remain potent activators of VEGFR-3. The cysteine at position 165 of SEQ ID NO: 24 is essential for binding either receptor, whereas analogs lacking the cysteines at  
20 positions 83 or 137 compete with native VEGF-C for binding with both receptors and stimulate both receptors.

VEGF-D is structurally and functionally most closely related to VEGF-C [see U.S. Patent 6,235,713 and International Patent Publ. No. WO 98/07832, incorporated herein by reference]. Like VEGF-C, VEGF-D is initially expressed as a  
25 prepro-peptide that undergoes N-terminal and C-terminal proteolytic processing, and forms non-covalently linked dimers. VEGF-D stimulates mitogenic responses in endothelial cells in vitro. During embryogenesis, VEGF-D is expressed in a complex temporal and spatial pattern, and its expression persists in the heart, lung, and skeletal muscles in adults. Isolation of a biologically active fragment of VEGF-D designated  
30 VEGF-D $\Delta$ N $\Delta$ C, is described in International Patent Publication No. WO 98/07832, incorporated herein by reference. VEGF-D $\Delta$ N $\Delta$ C consists of amino acid residues 93 to 201 of VEGF-D (SEQ ID NO: 26) optionally linked to the affinity tag peptide FLAG®, or other sequences.

The prepro-VEGF-D polypeptide has a putative signal peptide of 21 amino acids and is apparently proteolytically processed in a manner analogous to the processing of prepro-VEGF-C. A "recombinantly matured" VEGF-D lacking residues 1-92 and 202-354 of SEQ ID NO: 26 retains the ability to activate receptors VEGFR-2 and VEGFR-3, and appears to associate as non-covalently linked dimers. Thus, preferred VEGF-D polynucleotides include those polynucleotides that comprise a nucleotide sequence encoding amino acids 93-201 of SEQ ID NO: 26. The guidance provided above for introducing function-preserving modifications into VEGF-C polypeptides is also suitable for introducing function-preserving modifications into VEGF-D polypeptides.

Four additional members of the VEGF subfamily have been identified in poxviruses, which infect humans, sheep and goats. The orf virus-encoded VEGF-E and NZ2 VEGF are potent mitogens and permeability enhancing factors. Both show approximately 25% amino acid identity to mammalian VEGF-A, and are expressed as disulfide-linked homodimers. Infection by these viruses is characterized by pustular dermatitis which may involve endothelial cell proliferation and vascular permeability induced by these viral VEGF proteins. [Ferrara, J Mol Med 77:527-543 (1999); Stackner and Achen, Growth Factors 17:1-11 (1999)]. VEGF-like proteins have also been identified from two additional strains of the orf virus, D1701 [GenBank Acc. No. AF106020; described in Meyer et al., EMBO J 18:363-374 (1999)] and NZ10 [described in International Patent Application PCT/US99/25869, incorporated herein by reference]. These viral VEGF-like proteins have been shown to bind VEGFR-2 present on host endothelium, and this binding is important for development of infection and viral induction of angiogenesis [Meyer et al., EMBO J 18:363-374 (1999); International Patent Application PCT/US99/25869].

#### *PDGF/VEGF Receptors*

Seven cell surface receptors that interact with PDGF/VEGF family members have been identified. These include PDGFR- $\alpha$  (see e.g., GenBank Acc. No. NM006206), PDGFR- $\beta$  (see e.g., GenBank Acc. No. NM002609), VEGFR-1/Flt-1 (fms-like tyrosine kinase-1; GenBank Acc. No. X51602; De Vries et al., Science 255:989-991 (1992)); VEGFR-2/KDR/Flk-1 (kinase insert domain containing receptor/fetal liver kinase-1; GenBank Acc. Nos. X59397 (Flk-1) and L04947 (KDR); Terman et al., Biochem Biophys Res Comm 187:1579-1586 (1992); Matthews et al.,

Proc Natl Acad Sci USA 88:9026-9030 (1991)); VEGFR-3/Flt4 (fms-like tyrosine kinase 4; U.S. Patent Nos. 5,776,755 and GenBank Acc. No. X68203 and S66407; Pajusola et al., Oncogene 9:3545-3555 (1994)), neuropilin-1 (Gen Bank Acc. No. NM003873), and neuropilin-2 (Gen Bank Acc. No. NM003872). The two PDGF  
5 receptors mediate signaling of PDGFs as described above. VEGF121, VEGF165, VEGF-B, PlGF-1 and PlGF-2 bind VEGFR-1; VEGF121, VEGF145, VEGF165, VEGF-C, VEGF-D, VEGF-E, and NZ2 VEGF bind VEGFR-2; VEGF-C and VEGF-D bind VEGFR-3; VEGF165, VEGF-B, PlGF-2, and NZ2 VEGF bind neuropilin-1; and VEGF165, and VEGF145 bind neuropilin-2.[Neufeld et al., FASEB J 13:9-22  
10 (1999); Stacker and Achen, Growth Factors 17:1-11 (1999); Ortega et al., Fron Biosci 4:141-152 (1999); Zachary, Intl J Biochem Cell Bio 30:1169-1174 (1998); Petrova et al., Exp Cell Res 253:117-130 (1999); Gluzman-Poltorak et al., J. Biol. Chem. 275:18040-45 (2000)].

The PDGF receptors are protein tyrosine kinase receptors (PTKs) that  
15 contain five immunoglobulin-like loops in their extracellular domains. VEGFR-1, VEGFR-2, and VEGFR-3 comprise a subgroup of the PDGF subfamily of PTKs, distinguished by the presence of seven Ig domains in their extracellular domain and a split kinase domain in the cytoplasmic region. Both neuropilin-1 and neuropilin-2 are non-PTK VEGF receptors, with short cytoplasmic tails not currently known to  
20 possess downstream signaling capacity.

Several of the VEGF receptors are expressed as more than one isoform. A soluble isoform of VEGFR-1 lacking the seventh Ig-like loop, transmembrane domain, and the cytoplasmic region is expressed in human umbilical vein endothelial cells. This VEGFR-1 isoform binds VEGF-A with high affinity and  
25 is capable of preventing VEGF-A-induced mitogenic responses [Ferrara, J Mol Med 77:527-543 (1999); Zachary, Intl J Biochem Cell Bio 30:1169-1174 (1998)]. A C-terminal truncated form of VEGFR-2 has also been reported [Zachary, Intl J Biochem Cell Bio 30:1169-1174 (1998)]. In humans, there are two isoforms of the VEGFR-3 protein which differ in the length of their C-terminal ends. Studies suggest that the  
30 longer isoform is responsible for most of the biological properties of VEGFR-3.

The expression of VEGFR-1 occurs mainly in vascular endothelial cells, although some may be present on monocytes, trophoblast cells, and renal mesangial cells [Neufeld et al., FASEB J 13:9-22 (1999)]. High levels of VEGFR-1

mRNA are also detected in adult organs, suggesting that VEGFR-1 has a function in quiescent endothelium of mature vessels not related to cell growth. VEGFR-1  $-/-$  mice die in utero between day 8.5 and 9.5. Although endothelial cells developed in these animals, the formation of functional blood vessels was severely impaired, suggesting that VEGFR-1 may be involved in cell-cell or cell-matrix interactions associated with cell migration. Recently, it has been demonstrated that mice expressing a mutated VEGFR-1 in which only the tyrosine kinase domain was missing show normal angiogenesis and survival, suggesting that the signaling capability of VEGFR-1 is not essential. [Neufeld et al., FASEB J 13:9-22 (1999); Ferrara, J Mol Med 77:527-543 (1999)].

VEGFR-2 expression is similar to that of VEGFR-1 in that it is broadly expressed in the vascular endothelium, but it is also present in hematopoietic stem cells, megakaryocytes, and retinal progenitor cells [Neufeld et al., FASEB J 13:9-22 (1999)]. Although the expression pattern of VEGFR-1 and VEGFR-2 overlap extensively, evidence suggests that, in most cell types, VEGFR-2 is the major receptor through which most of the VEGFs exert their biological activities. Examination of mouse embryos deficient in VEGFR-2 further indicate that this receptor is required for both endothelial cell differentiation and the development of hematopoietic cells [Joukov et al., J Cell Physiol 173:211-215 (1997)].

VEGFR-3 is expressed broadly in endothelial cells during early embryogenesis. During later stages of development, the expression of VEGFR-3 becomes restricted to developing lymphatic vessels [Kaipainen, A., et al., Proc. Natl. Acad. Sci. USA, 92: 3566-3570 (1995)]. In adults, the lymphatic endothelia and some high endothelial venules express VEGFR-3, and increased expression occurs in lymphatic sinuses in metastatic lymph nodes and in lymphangioma. VEGFR-3 is also expressed in a subset of CD34+ hematopoietic cells which may mediate the myelopoietic activity of VEGF-C demonstrated by overexpression studies [WO 98/33917]. Targeted disruption of the VEGFR-3 gene in mouse embryos leads to failure of the remodeling of the primary vascular network, and death after embryonic day 9.5 [Dumont et al., Science, 282: 946-949 (1998)]. These studies suggest an essential role for VEGFR-3 in the development of the embryonic vasculature, and also during lymphangiogenesis.

Structural analyses of the VEGF receptors indicate that the VEGF-A binding site on VEGFR-1 and VEGFR-2 is located in the second and third Ig-like loops. Similarly, the VEGF-C and VEGF-D binding sites on VEGFR-2 and VEGFR-3 are also contained within the second Ig-loop [Taipale et al., Curr Top Microbiol Immunol 237:85-96 (1999)]. The second Ig-like loop also confers ligand specificity as shown by domain swapping experiments [Ferrara, J Mol Med 77:527-543 (1999)]. Receptor-ligand studies indicate that dimers formed by the VEGF family proteins are capable of binding two VEGF receptor molecules, thereby dimerizing VEGF receptors. The fourth Ig-like loop on VEGFR-1, and also possibly on VEGFR-2, acts as the receptor dimerization domain that links two receptor molecules upon binding of the receptors to a ligand dimer [Ferrara, J Mol Med 77:527-543 (1999)]. Although the regions of VEGF-A that bind VEGFR-1 and VEGFR-2 overlap to a large extent, studies have revealed two separate domains within VEGF-A that interact with either VEGFR-1 or VEGFR-2, as well as specific amino acid residues within these domains that are critical for ligand-receptor interactions. Mutations within either VEGF receptor-specific domain that specifically prevent binding to one particular VEGF receptor have also been recovered [Neufeld et al., FASEB J 13:9-22 (1999)].

VEGFR-1 and VEGFR-2 are structurally similar, share common ligands (VEGF<sub>121</sub> and VEGF<sub>165</sub>), and exhibit similar expression patterns during development. However, the signals mediated through VEGFR-1 and VEGFR-2 by the same ligand appear to be slightly different. VEGFR-2 has been shown to undergo autophosphorylation in response to VEGF-A, but phosphorylation of VEGFR-1 under identical conditions was barely detectable. VEGFR-2 mediated signals cause striking changes in the morphology, actin reorganization, and membrane ruffling of porcine aortic endothelial cells recombinantly overexpressing this receptor. In these cells, VEGFR-2 also mediated ligand-induced chemotaxis and mitogenicity; whereas VEGFR-1-transfected cells lacked mitogenic responses to VEGF-A. Mutations in VEGF-A that disrupt binding to VEGFR-2 fail to induce proliferation of endothelial cells, whereas VEGF-A mutants that are deficient in binding VEGFR-1 are still capable of promoting endothelial proliferation. Similarly, VEGF stimulation of cells expressing only VEGFR-2 leads to a mitogenic response whereas comparable stimulation of cells expressing only VEGFR-1 also results in cell migration, but does not induce cell proliferation. In addition, phosphoproteins co-precipitating with

VEGFR-1 and VEGFR-2 are distinct, suggesting that different signaling molecules interact with receptor-specific intracellular sequences.

The emerging hypothesis is that the primary function of VEGFR-1 in angiogenesis may be to negatively regulate the activity of VEGF-A by binding it and thus preventing its interaction with VEGFR-2, whereas VEGFR-2 is thought to be the main transducer of VEGF-A signals in endothelial cells. In support of this hypothesis, mice deficient in VEGFR-1 die as embryos while mice expressing a VEGFR-1 receptor capable of binding VEGF-A but lacking the tyrosine kinase domain survive and do not exhibit abnormal embryonic development or angiogenesis. In addition, analyses of VEGF-A mutants that bind only VEGFR-2 show that they retain the ability to induce mitogenic responses in endothelial cells. However, VEGF-mediated migration of monocytes is dependent on VEGFR-1, indicating that signaling through this receptor is important for at least one biological function. In addition, the ability of VEGF-A to prevent the maturation of dendritic cells is also associated with VEGFR-1 signaling, suggesting that VEGFR-1 may function in cell types other than endothelial cells. [Ferrara, J Mol Med 77:527-543 (1999); Zachary, Intl J Biochem Cell Bio 30:1169-1174 (1998)].

With respect to the neuropilins or other polypeptides used to practice the invention, it will be understood that native sequences will usually be most preferred. By "native sequences" is meant sequences encoded by naturally occurring polynucleotides, including but not limited to prepro-peptides, pro-peptides, and partially and fully proteolytically processed polypeptides. As described above, many of the polypeptides have splice variants that exist, e.g., due to alternative RNA processing, and such splice variants comprise native sequences. For purposes described herein, fragments of the foregoing that retain the binding properties of interest also shall be considered native sequences. Moreover, modifications can be made to most protein sequences without destroying the activity of interest of the protein, especially conservative amino acid substitutions, and proteins so modified are also suitable for practice of the invention. By "conservative amino acid substitution" is meant substitution of an amino acid with an amino acid having a side chain of a similar chemical character. Similar amino acids for making conservative substitutions include those having an acidic side chain (glutamic acid, aspartic acid); a basic side chain (arginine, lysine, histidine); a polar amide side chain (glutamine, asparagine); a

hydrophobic, aliphatic side chain (leucine, isoleucine, valine, alanine, glycine); an aromatic side chain (phenylalanine, tryptophan, tyrosine); a small side chain (glycine, alanine, serine, threonine, methionine); or an aliphatic hydroxyl side chain (serine, threonine).

5                   Moreover, deletion and addition of amino acids is often possible without destroying a desired activity. With respect to the present invention, where binding activity is of particular interest and the ability of molecules to activate or inhibit receptor tyrosine kinases upon binding is of special interest, binding assays and tyrosine phosphorylation assays are available to determine whether a particular  
10   ligand or ligand variant (a) binds and (b) stimulates or inhibits RTK activity.

Two manners for defining genera of polypeptide variants include percent amino acid identity to a native polypeptide (e.g., 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity preferred), or the ability of encoding-polynucleotides to hybridize to each other under specified conditions. One exemplary set of conditions  
15   is as follows: hybridization at 42°C in 50% formamide, 5X SSC, 20 mM Na<sub>2</sub>PO<sub>4</sub>, pH 6.8; and washing in 1X SSC at 55°C for 30 minutes. Formula for calculating equivalent hybridization conditions and/or selecting other conditions to achieve a desired level of stringency are well known. It is understood in the art that conditions of equivalent stringency can be achieved through variation of temperature and buffer,  
20   or salt concentration as described Ausubel, et al. (Eds.), *Protocols in Molecular Biology*, John Wiley & Sons (1994), pp. 6.0.3 to 6.4.10. Modifications in hybridization conditions can be empirically determined or precisely calculated based on the length and the percentage of guanosine/cytosine (GC) base pairing of the probe. The hybridization conditions can be calculated as described in Sambrook, et  
25   al., (Eds.), *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press: Cold Spring Harbor, New York (1989), pp. 9.47 to 9.51.

#### B.     Gene Therapy

While much of the application, including the examples, are written in the context of protein-protein interactions and protein administration, it should be  
30   clear that genetic manipulations to achieve modulation of protein expression or activity is specifically contemplated. For example, where administration of proteins is contemplated, administration of a gene therapy vector to cause the protein of interest to be produced in vivo also is contemplated. Where inhibition of proteins is



contemplated (e.g., through use of antibodies or small molecule inhibitors), inhibition of protein expression in vivo by genetic techniques, such as knock-out techniques or anti-sense therapy, is contemplated.

Any suitable vector may be used to introduce a transgene of interest  
5 into an animal. Exemplary vectors that have been described in the literature include replication-deficient retroviral vectors, including but not limited to lentivirus vectors [Kim et al., *J. Virol.*, 72(1): 811-816 (1998); Kingsman & Johnson, *Scrip Magazine*, October, 1998, pp. 43-46.]; adeno-associated viral vectors [Gnatenko et al., *J. Investig. Med.*, 45: 87-98 (1997)]; adenoviral vectors [See, e.g., U.S. Patent No.  
10 5,792,453; Quantin et al., *Proc. Natl. Acad. Sci. USA*, 89: 2581-2584 (1992); Stratford-Perricadet et al., *J. Clin. Invest.*, 90: 626-630 (1992); and Rosenfeld et al., *Cell*, 68: 143-155 (1992)]; Lipofectin-mediated gene transfer (BRL); liposomal vectors [See, e.g., U.S. Patent No. 5,631,237 (Liposomes comprising Sendai virus proteins)] ; and combinations thereof. All of the foregoing documents are  
15 incorporated herein by reference in the entirety. Replication-deficient adenoviral vectors and adeno-associated viral vectors constitute preferred embodiments.

In embodiments employing a viral vector, preferred polynucleotides include a suitable promoter and polyadenylation sequence to promote expression in the target tissue of interest. For many applications of the present invention, suitable  
20 promoters/enhancers for mammalian cell expression include, e.g., cytomegalovirus promoter/enhancer [Lehner et al., *J. Clin. Microbiol.*, 29:2494-2502 (1991); Boshart et al., *Cell*, 41:521-530 (1985)]; Rous sarcoma virus promoter [Davis et al., *Hum. Gene Ther.*, 4:151 (1993)]; or simian virus 40 promoter.

Anti-sense polynucleotides are polynucleotides which recognize and  
25 hybridize to polynucleotides encoding a protein of interest and can therefore inhibit transcription or translation of the protein. Full length and fragment anti-sense polynucleotides may be employed. Commercial software is available to optimize antisense sequence selection and also to compare selected sequences to known genomic sequences to help ensure uniqueness/specificity for a chosen gene. Such  
30 uniqueness can be further confirmed by hybridization analyses. Antisense nucleic acids (preferably 10 to 20 base pair oligonucleotides) are introduced into cells (e.g., by a viral vector or colloidal dispersion system such as a liposome). The antisense nucleic acid binds to the target nucleotide sequence in the cell and prevents

transcription or translation of the target sequence. Phosphorothioate and methylphosphonate antisense oligonucleotides are specifically contemplated for therapeutic use by the invention. The antisense oligonucleotides may be further modified by poly-L-lysine, transferrin polylysine, or cholesterol moietyneuropilins at their 5' end.

Genetic control can also be achieved through the design of novel transcription factors for modulating expression of the gene of interest in native cells and animals. For example, the Cys2-His2 zinc finger proteins, which bind DNA via their zinc finger domains, have been shown to be amenable to structural changes that lead to the recognition of different target sequences. These artificial zinc finger proteins recognize specific target sites with high affinity and low dissociation constants, and are able to act as gene switches to modulate gene expression. Knowledge of the particular target sequence of the present invention facilitates the engineering of zinc finger proteins specific for the target sequence using known methods such as a combination of structure-based modeling and screening of phage display libraries [Segal et al., (1999) Proc Natl Acad Sci USA 96:2758-2763; Liu et al., (1997) Proc Natl Acad Sci USA 94:5525-30; Greisman and Pabo (1997) Science 275:657-61; Choo et al., (1997) J Mol Biol 273:525-32]. Each zinc finger domain usually recognizes three or more base pairs. Since a recognition sequence of 18 base pairs is generally sufficient in length to render it unique in any known genome, a zinc finger protein consisting of 6 tandem repeats of zinc fingers would be expected to ensure specificity for a particular sequence [Segal et al., (1999) Proc Natl Acad Sci USA 96:2758-2763]. The artificial zinc finger repeats, designed based on target sequences, are fused to activation or repression domains to promote or suppress gene expression [Liu et al., (1997) Proc Natl Acad Sci USA 94:5525-30]. Alternatively, the zinc finger domains can be fused to the TATA box-binding factor (TBP) with varying lengths of linker region between the zinc finger peptide and the TBP to create either transcriptional activators or repressors [Kim et al., (1997) Proc Natl Acad Sci USA 94:3616-3620]. Such proteins, and polynucleotides that encode them, have utility for modulating expression in vivo in both native cells, animals and humans. The novel transcription factor can be delivered to the target cells by transfecting constructs that express the transcription factor (gene therapy), or by introducing the protein. Engineered zinc finger proteins can also be designed to bind RNA sequences

for use in therapeutics as alternatives to antisense or catalytic RNA methods [McColl et al., (1999) Proc Natl Acad Sci USA 96:9521-6; Wu et al., (1995) Proc Natl Acad Sci USA 92:344-348].

### C. Antibodies

5                   Antibodies are useful for modulating Neuropilin-VEGF-C interactions due to the ability to easily generate antibodies with relative specificity, and due to the continued improvements in technologies for adopting antibodies to human therapy. Thus, the invention contemplates use of antibodies (e.g., monoclonal and polyclonal antibodies, single chain antibodies, chimeric antibodies, bifunctional/bispecific  
10 antibodies, humanized antibodies, human antibodies, and complementary determining region (CDR)-grafted antibodies, including compounds which include CDR sequences which specifically recognize a polypeptide of the invention) specific for polypeptides of interest to the invention, especially neuropilins, VEGF receptors, and VEGF-C and VEGF-D proteins. Preferred antibodies are human antibodies which are  
15 produced and identified according to methods described in WO93/11236, published June 20, 1993, which is incorporated herein by reference in its entirety. Antibody fragments, including Fab, Fab', F(ab')<sub>2</sub>, and Fv, are also provided by the invention. The term "specific for," when used to describe antibodies of the invention, indicates that the variable regions of the antibodies of the invention recognize and bind the  
20 polypeptide of interest exclusively (i.e., able to distinguish the polypeptides of interest from other known polypeptides of the same family, by virtue of measurable differences in binding affinity, despite the possible existence of localized sequence identity, homology, or similarity between family members). It will be understood that specific antibodies may also interact with other proteins (for example, *S. aureus*  
25 protein A or other antibodies in ELISA techniques) through interactions with sequences outside the variable region of the antibodies, and in particular, in the constant region of the molecule. Screening assays to determine binding specificity of an antibody of the invention are well known and routinely practiced in the art. For a comprehensive discussion of such assays, see Harlow et al. (Eds), *Antibodies A Laboratory Manual*; Cold Spring Harbor Laboratory; Cold Spring Harbor, NY  
30 (1988), Chapter 6. Antibodies of the invention can be produced using any method well known and routinely practiced in the art.

Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for NRP-2, the other one is for an NRP-2 binding partner, and preferably for a cell-surface protein or receptor or  
5 receptor subunit, such as VEGFR-3.

In one embodiment, a bispecific antibody which binds to both NRP-2 and VEGFR-3 is used to modulate the growth, migration or proliferation of cells that results from the interaction of VEGF-C with VEGFR-3. For example, the bispecific antibody is administered to an individual having tumors characterized by lymphatic  
10 metastasis or other types of tumors expressing both VEGF-C and VEGFR-3, and NRP-2. The bispecific antibody which binds both NRP-2 and VEGFR-3 blocks the binding of VEGF-C to VEGFR-3, thereby interfering with VEGF-C mediated lymphangiogenesis and slowing the progression of tumor metastasis. In another embodiment, the same procedure is carried out with a bispecific antibody which binds  
15 to NRP-2 and VEGF-C, wherein administration of said antibody sequesters soluble VEGF-C and prevents its binding to VEGFR-3, effectively acting as an inhibitor of VEGF-C mediated signaling through VEGFR-3.

Bispecific antibodies are produced, isolated, and tested using standard procedures that have been described in the literature. See, e.g., Pluckthun & Pack,  
20 Immunotechnology, 3:83-105 (1997); Carter et al., J. Hematotherapy, 4: 463-470 (1995); Renner & Pfreundschuh, Immunological Reviews, 1995, No. 145, pp. 179-209; Pfreundschuh U.S. Patent No. 5,643,759; Segal et al., J. Hematotherapy, 4: 377-382 (1995); Segal et al., Immunobiology, 185: 390-402 (1992); and Bolhuis et al., Cancer Immunol. Immunother., 34: 1-8 (1991), all of which are incorporated herein  
25 by reference in their entireties.

The term "bispecific antibody" refers to a single, divalent antibody which has two different antigen binding sites (variable regions). As described below, the bispecific binding agents are generally made of antibodies, antibody fragments, or analogs of antibodies containing at least one complementarity determining region  
30 derived from an antibody variable region. These may be conventional bispecific antibodies, which can be manufactured in a variety of ways (Holliger, P. and Winter G. Current Opinion Biotechnol. 4, 446-449 (1993)), e.g. prepared chemically, using hybrid hybridomas, via linking the coding sequence of such a bispecific antibody into

a vector and producing the recombinant peptide or by phage display. The bispecific antibodies may also be any bispecific antibody fragments.

In one method, bispecific antibodies fragments are constructed by converting whole antibodies into (monospecific)  $F(ab')_2$  molecules by proteolysis, splitting these fragments into the Fab' molecules and recombine Fab' molecules with different specificity to bispecific  $F(ab')_2$  molecules (see, for example, U.S. Patent 5,798,229).

A bispecific antibody can be generated by enzymatic conversion of two different monoclonal antibodies, each comprising two identical L (light chain)-H (heavy chain) half molecules and linked by one or more disulfide bonds, into two  $F(ab')_2$  molecules, splitting each  $F(ab')_2$  molecule under reducing conditions into the Fab' thiols, derivatizing one of these Fab' molecules of each antibody with a thiol activating agent and combining an activated Fab' molecule bearing NRP-2 specificity with a non-activated Fab' molecule bearing an NRP-2 binding partner specificity or vice versa in order to obtain the desired bispecific antibody  $F(ab')_2$  fragment.

As enzymes suitable for the conversion of an antibody into its  $F(ab')_2$  molecules, pepsin and papain may be used. In some cases, trypsin or bromelain are suitable. The conversion of the disulfide bonds into the free SH-groups (Fab' molecules) may be performed by reducing compounds, such as dithiothreitol (DTT), mercaptoethanol, and mercaptoethylamine. Thiol activating agents according to the invention which prevent the recombination of the thiol half-molecules, are 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB), 2,2'-dipyridinedisulfide, 4,4'-dipyridinedisulfide or tetrathionate/sodium sulfite (see also Raso et al., Cancer Res., 42:457 (1982), and references incorporated therein).

The treatment with the thiol-activating agent is generally performed only with one of the two Fab' fragments. Principally, it makes no difference which one of the two Fab' molecules is converted into the activated Fab' fragment (e.g., Fab'-TNB). Generally, however, the Fab' fragment being more labile is modified with the thiol-activating agent. In the present case, the fragments bearing the anti-tumor specificity are slightly more labile, and, therefore, preferably used in the process. The conjugation of the activated Fab' derivative with the free hinge-SH groups of the second Fab' molecule to generate the bivalent  $F(ab')_2$  antibody occurs spontaneously

at temperatures between 0° and 30° C. The yield of purified F(ab').sub.2 antibody is 20-40% (starting from the whole antibodies).

Another method for producing bispecific antibodies is by the fusion of two hybridomas to form a hybrid hybridoma. As used herein, the term "hybrid  
5 hybridoma" is used to describe the productive fusion of two B cell hybridomas. Using now standard techniques, two antibody producing hybridomas are fused to give daughter cells, and those cells that have maintained the expression of both sets of clonotype immunoglobulin genes are then selected.

To identify the bispecific antibody standard methods such as ELISA  
10 are used wherein the wells of microtiter plates are coated with a reagent that specifically interacts with one of the parent hybridoma antibodies and that lacks cross-reactivity with both antibodies. In addition, FACS, immunofluorescence staining, idiotype specific antibodies, antigen binding competition assays, and other methods common in the art of antibody characterization may be used in conjunction with the  
15 present invention to identify preferred hybrid hybridomas.

Bispecific molecules of this invention can also be prepared by conjugating a gene encoding a binding specificity for NRP-2 to a gene encoding at least the binding region of an antibody chain which recognizes a binding partner of NRP-2 such as VEGF-C or VEGFR-3. This construct is transfected into a host cell  
20 (such as a myeloma) which constitutively expresses the corresponding heavy or light chain, thereby enabling the reconstitution of a bispecific, single-chain antibody, two-chain antibody (or single chain or two-chain fragment thereof such as Fab) having a binding specificity for NRP-2 and for a NRP-2 binding partner. Construction and cloning of such a gene construct can be performed by standard procedures.

25 Bispecific antibodies are also generated via phage display screening methods using the so-called hierarchical dual combinatorial approach as disclosed in WO 92/01047 in which an individual colony containing either an H or L chain clone is used to infect a complete library of clones encoding the other chain (L or H) and the resulting two-chain specific binding member is selected in accordance with phage  
30 display techniques such as those described therein. This technique is also disclosed in Marks et al, (Bio/Technology, 1992, 10:779-783).

The bispecific antibody fragments of the invention can be administered to human patients for therapy. Thus, in one embodiment the bispecific antibody is provided with a pharmaceutical formulation comprising as active ingredient at least one bispecific antibody fragment as defined above, associated with one or more  
5 pharmaceutically acceptable carrier, excipient or diluent. In another embodiment, the compound further comprises an anti-neoplastic or cytotoxic agent conjugated to the bispecific antibody.

Recombinant antibody fragments, e.g. scFvs, can also be engineered to assemble into stable multimeric oligomers of high binding avidity and specificity to  
10 different target antigens. Such diabodies (dimers), triabodies (trimers) or tetrabodies (tetramers) are well known within the art and have been described in the literature, see e.g. Kortt et al., *Biomol Eng.* 2001 Oct 15;18(3):95-108 and Todorovska et al., *J Immunol Methods.* 2001 Feb 1;248(1-2):47-66.

Non-human antibodies may be humanized by any methods known in  
15 the art. In one method, the non-human CDRs are inserted into a human antibody or consensus antibody framework sequence. Further changes can then be introduced into the antibody framework to modulate affinity or immunogenicity.

#### D. Dosing

Some methods of the invention include a step of polypeptide  
20 administration to a human or animal. Polypeptides may be administered in any suitable manner using an appropriate pharmaceutically-acceptable vehicle, e.g., a pharmaceutically-acceptable diluent, adjuvant, excipient or carrier. The composition to be administered according to methods of the invention preferably comprises (in addition to the polynucleotide or vector) a pharmaceutically-acceptable carrier  
25 solution such as water, saline, phosphate-buffered saline, glucose, or other carriers conventionally used to deliver therapeutics or imaging agents.

The "administering" that is performed according to the present invention may be performed using any medically-accepted means for introducing a therapeutic directly or indirectly into a mammalian subject, including but not limited to  
30 injections (e.g., intravenous, intramuscular, subcutaneous, or catheter); oral ingestion; intranasal or topical administration; and the like. For some cardiovascular diseases a preferred route of administration is intravascular, such as by intravenous,

intra-arterial, or intracoronary arterial injection. In one embodiment, administering the composition is performed at the site of a lesion or affected tissue needing treatment by direct injection into the lesion site or via a sustained delivery or sustained release mechanism, which can deliver the formulation internally. For example, biodegradable microspheres or capsules or other biodegradable polymer configurations capable of sustained delivery of a composition (e.g., a soluble polypeptide, antibody, or small molecule) can be included in the formulations of the invention implanted near the lesion.

The therapeutic composition may be delivered to the patient at multiple sites. The multiple administrations may be rendered simultaneously or may be administered over a period of several hours. In certain cases it may be beneficial to provide a continuous flow of the therapeutic composition. Additional therapy may be administered on a period basis, for example, daily, weekly or monthly.

Polypeptides for administration may be formulated with uptake or absorption enhancers to increase their efficacy. Such enhancer include for example, salicylate, glycocholate/linoleate, glycholate, aprotinin, bacitracin, SDS caprate and the like. See, e.g., Fix (J. Pharm. Sci., 85(12) 1282-1285, 1996) and Oliyai and Stella (Ann. Rev. Pharmacol. Toxicol., 32:521-544, 1993).

The amounts of peptides in a given dosage will vary according to the size of the individual to whom the therapy is being administered as well as the characteristics of the disorder being treated. In exemplary treatments, it may be necessary to administer about 50mg/day, 75 mg/day, 100mg/day, 150mg/day, 200mg/day, 250 mg/day. These concentrations may be administered as a single dosage form or as multiple doses. Standard dose-response studies, first in animal models and then in clinical testing, reveal optimal dosages for particular disease states and patient populations.

It will also be apparent that dosing should be modified if traditional therapeutics are administered in combination with therapeutics of the invention. For example, treatment of cancer using traditional chemotherapeutic agents or radiation, in combination with methods of the invention, is contemplated.

E. Kits



As an additional aspect, the invention includes kits which comprise one or more compounds or compositions of the invention packaged in a manner which facilitates their use to practice methods of the invention. In a simplest embodiment, such a kit includes a compound or composition described herein as  
5 useful for practice of a method of the invention (e.g., polynucleotides or polypeptides for administration to a person or for use in screening assays), packaged in a container such as a sealed bottle or vessel, with a label affixed to the container or included in the package that describes use of the compound or composition to practice the method of the invention. Preferably, the compound or composition is packaged in a unit  
10 dosage form. The kit may further include a device suitable for administering the composition according to a preferred route of administration or for practicing a screening assay.

Additional aspects and details of the invention will be apparent from the following examples, which are intended to be illustrative rather than limiting.

15

#### **EXAMPLE 1**

##### **VEGF-C ISOFORMS BIND TO NEUROPILIN-2 AND NEUROPILIN-1**

The following experiments demonstrated that VEGF-C isoforms interact with the neuropilin family members, neuropilin-2 and neuropilin-1.

#### 20 A. Materials

To investigate the binding of neuropilin-2 to VEGF-C the following constructs were either made or purchased from commercial sources:

a) Cloning of the NRP-2/IgG expression vector. The extracellular domain of hNRP-2 was cloned into the pIgplus vector in frame with the human IgG1  
25 Fc tail as follows. Full-length NRP-2 cDNA (SEQ ID NO. 3) was assembled from several IMAGE Consortium cDNA Clones (Incyte Genomics) (Fig. 1A). The Image clones used are marked as 2A (GenBank Acc. No AA621145; Clone ID 1046499), 3 (AA931763; 1564852), 4 (AA127691; 490311), and 5 (AW296186; 2728688); these clones were confirmed by sequencing. Image clones 4 and 5 differ due to alternative  
30 splicing, coding for a17 and a22 isoforms, respectively. The BamHI-NotI fragment from the image clone 3 was first cloned into the pcDNA3.1z+ vector (Invitrogen), and fragments KpnI-BglII from clone 2A and BglII-BamHI from clone 3 were then added

to obtain the 5' region (bp 1-2188). NotI-BamHI fragments from clones 4 and 5 were separately transferred into the pIgplus vector, and the KpnI-NotI fragment from the pcDNA3.1z+ vector was then inserted to obtain the expression vector coding for the extracellular domain of the hNRP-2/IgG fusion protein (SEQ ID NO. 3, positions 1 to 2577). The NRP-2 inserts in the resulting vectors were sequenced. The Image clone 3 codes for one amino acid different from the GenBank Sequence (AAA 1804-1806 GAG | K602E). However, the amino acid sequence in the Image clone 3 is identical to the original sequence published by Chen et al. (Chen et al., Neuron, 19:547. 1997).

b) a VEGFR-3-Fc construct, in which an extracellular domain portion of VEGFR-3 comprising the first three immunoglobulin-like domains (SEQ ID NO. 32, amino acids 1 to 329) was fused to the Fc portion of human IgG1 [see Makinen et al., Nat Med., 7:199-205 (2001)]. Full length VEGFR-3 cDNA and amino acid sequences are set forth in SEQ. ID NOS: 31 and 32.

c) a NRP-1-Fc construct, in which an extracellular domain portion of murine NRP-1 (base pairs 248-2914 of SEQ. ID NO: 5) was fused to the Fc portion of human IgG1 (Makinen et al, J. Biol.Chem 274:21217-222. 1999); and

d) the expression vectors, in pREP7 backbone, encoding either VEGF<sub>165</sub> (Genbank Accession No. M32997) or full-length VEGF-C (SEQ. ID NO:24), have been described recently (Olofsson et al., Proc. Natl. Acad. Sci. USA 93: 2576-81. 1996; and Joukov et al., EMBO J. 15: 290-298. 1996).

#### B. Co-immunoprecipitation of VEGF-C with NRP-2

The NRP-2, NRP-1, and VEGFR-3 pIgplus fusion constructs were transfected into 293T cells using the FUGENETM6 transfection reagent (Roche Molecular Biochemicals). The cells were grown in Dulbecco's modified Eagle's medium supplemented with 10% fetal calf serum (Gibco BRL), glutamine, and antibiotics. The media was replaced 48 h after transfection by DMEM containing 0.2% BSA and collected after 20 h.

For growth factor production, 293EBNA cells were transfected with expression vectors coding for VEGF<sub>165</sub>, prepro-VEGF-C, or empty vector (Mock). 36 h after transfection, the cells were first incubated in methionine and cysteine free MEM (Gibco BRL) for 45 min, metabolically labeled in the same medium

supplemented with 100 millicurie [mCi]/ml Pro-mix [35S] (Amersham) for 6-7 h (1 mCi=37 kBq) containing radiolabelled methionine and cysteine.

For immunoprecipitation controls, 1 ml of the labeled medium was incubated with either MAB 293 monoclonal anti-VEGF-Ab (R&D Systems), or rabbit  
5 antiserum 882 against VEGF-C (Joukov et al., EMBO J. 16:3898-3911. 1997) for 2 h, with rotation, at +4° C. Protein A-Sepharose (Pharmacia) was then added, and incubated overnight. The immunoprecipitates were washed two times with ice-cold PBS-0.5% Tween 20, heated in Laemmli sample buffer, and electrophoresed in 15% SDS PAGE. The gel was dried and exposed to Kodak Biomax MR film.

10 For binding experiments, the labeled supernatants from the Mock- or VEGF-C transfected cells were first immunoprecipitated with VEGF antibodies (R & D Systems) for depletion of endogenous VEGF. 4 ml of hNRP-2 a17-IgG or 1 ml of VEGFR-3-IgG or NRP-1-IgG fusion protein containing media were incubated with 1 ml of growth factor containing media (Mock, VEGF or VEGF-C) in binding buffer  
15 (0.5% BSA, 0.02% Tween 20) for 2 h, Protein A-Sepharose was added, and incubated overnight. The samples were then washed once with ice-cold binding buffer and three times with PBS and subjected to 15% SDS PAGE. The radiolabeled VEGF-C polypeptide was detected via chemiluminescence (ECL).

Results show that both the 29 kD and 21-23 kD isoforms of VEGF-C  
20 bind to NRP-2 while only the 29 kD form binds to NRP-1. VEGFR-3 binding to VEGF-C was used as a positive control for VEGF-C binding in the assay. It has been shown previously that heparin strongly increases VEGF binding to NRP-2 (Gluzman-Poltorak et al., J. Biol.Chem. 275: 18040-045. 2000). Addition of heparin to the assay mixture illustrates that VEGF<sub>165</sub> binding to NRP-2 is heparin dependent while  
25 VEGF<sub>165</sub> binding to NRP-1 is independent of heparin binding, and the presence of heparin has no effect on VEGF-C binding to any of its receptors.

C. Cell-based assay using cells that naturally express Neuropilin receptors.

The preceding experiment can be modified by substituting cells that naturally express a neuropilin receptor (especially NRP-2) for the transfected  
30 293EBNA cells. Use of primary cultures of neuronal cells expressing neuropilin receptors is specifically contemplated, e.g., cultured cerebellar granule cells derived from embryos. Additionally, NRP-receptor-specific antibodies can be employed to

identify other cells (e.g., cells involved in the vasculature), such as human microvascular endothelial cells (HMVEC), human cutaneous fat pad microvascular cells (HUVEC) that express NRP receptors.

5

## EXAMPLE 2 NEUROPILIN-2 INTERACTS WITH VEGFR-3

Recent results indicate that NRP-1 is a co-receptor for VEGF<sub>165</sub> binding, forming a complex with VEGFR-2, which results in enhanced VEGF<sub>165</sub> signaling through VEGFR-2, over VEGF<sub>165</sub> binding to VEGFR-2 alone, thereby enhancing the biological responses to this ligand (Soker et al., Cell 92: 735-45. 1998). A similar phenomenon may apply to VEGF-C signaling via possible VEGFR-3/NRP-2 receptor complexes.

### A. Binding Assay

The NRP-2(a22) expression vector was cloned as described in Example 1 (Fig. 1B) with the addition of a detectable tag on the 3' end. For 3' end construction, the Not I-Bam HI fragment (clone 5) was then constructed by PCR, introducing the V5 tag (GKPIPNPLLGLDST) (SEQ ID NO:33) and a stop codon to the 3' terminus. To obtain the expression vector coding for the full-length hNRP-2(a22) protein, this 3' end was then transferred into the vector containing the 5' fragment. The resulting clone was referred to as V5 NRP-2.

To determine the interaction of VEGFR-3 with NRP-2, 10 cm plates of human embryonic kidney cells (293T or 293EBNA) were transfected with the V5 NRP-2 construct or VEGFR-3 using 6 µl of FUGENE TM6 (Roche Molecular Biochemicals, Indianapolis, Indiana) and 2 µg DNA. The cells were grown in Dulbecco's modified Eagle's medium supplemented with 10% fetal calf serum (Gibco BRL), glutamine, and antibiotics. For Mock transfections, 2 µg of empty vector was used. For single receptor transfections, the VEGFR-3-myc/pcDNA3.1 (Karkkainen et al, Nat. Genet. 25:153-59. 2000) or NRP-2(a22)/pcDNA3.1z+and empty vector were used in a one to one ratio. The VEGFR-3/NRP-2 co-transfections were also made in a one to one ratio. After 24 h, the 293EBNA cells were starved overnight, and stimulated for 10 min using 300 ng/ml ΔNΔCVEGF-C (produced in *P. pastoris*; (Joukov et al. EMBOJ. 16: 3898-3911. 1997)). The cells were then washed twice with ice-cold PBS containing vanadate (100 µM) and PMSF (100 µM), and lysed in

dimerization lysis buffer (20 mM HEPES pH 7.5, 150 mM NaCl, 10% glycerol, 1% Triton X-100, 2 mM MgCl<sub>2</sub>, 2 mM CaCl<sub>2</sub>, 10 µg/ml bovine serum albumin (BSA)) containing 2 mM vanadate, 1 mM PMSF, 0.07 U/ml aprotinin, and 4 µg/ml leupeptin. The lysates were cleared by centrifugation for 10 min at 19,000g, and incubated with antibodies for VEGFR-3 (9d9F; (Jussila et al., Cancer Res. 58: 1599-1604. 1998)), or V5 (Invitrogen) for 5 h at +4 °C. The immunocomplexes were then incubated with protein A-Sepharose (Pharmacia) overnight at +4 °C, the immunoprecipitates were washed four times with dimerization lysis buffer without BSA, and the samples subjected to 7.5% SDS-PAGE in reducing conditions. The proteins were transferred to a Protran nitrocellulose filter (Schleicher & Schuell) using semi-dry transfer apparatus. After blocking with 5% non-fat milk powder in TBS-T buffer (10 mM Tris pH 7.5, 150 mM NaCl, 0.1% Tween 20), the filters were incubated with the V5 antibodies, followed by HRP-conjugated rabbit-anti-mouse immunoglobulins (Dako), and visualized using enhanced chemiluminescence (ECL).

Co-immunoprecipitation of VEGFR-3 and NRP-2 constructs transfected into 293T cells demonstrates that NRP-2 interacts with VEGFR-3 when co-expressed in the same cell. Immunoprecipitation after the addition of VEGF-C to the cell culture media shows that the NRP-2/VEGFR-3 interaction is not dependent on the presence of the VEGF-C ligand, implying that these receptors may associate naturally in vivo without the presence of VEGF-C. This finding may have tremendous implications on the binding and activity of VEGF-C during angiogenesis. VEGF-C, an integral molecule in promoting growth and development of the lymphatic vasculature, is also highly involved in the metastasis of cancerous cells through the lymph system and apparently the neovascularization of at least some solid tumors (see International Patent Publication No. WO 00/21560). The novel interaction between neuropilins and VEGF-C provides for a means to specifically block this lymphatic growth into solid tumors by inhibiting lymphatic cell migration as a result of VEGF-C binding to VEGFR-3. Neuropilins-1 and-2 are the only VEGF receptors at the surface of some tumor cells, indicating the binding of VEGF to neuropilins is relevant to tumor growth (Soker et al, Cell 92: 735-45. 1998) and that VEGF-C binding to neuropilin-2 may be a means to specifically target tumor metastasis through the lymphatic system.

### EXAMPLE 3

#### INHIBITION OF VEGF-C BINDING TO VEGFR-3 BY NEUROPILINS

The binding affinity between VEGF-C and neuropilin receptor molecules provides therapeutic indications for modulators of VEGF-C-induced VEGFR-3 receptor signaling, in order to modulate, i.e. stimulate or inhibit, VEGF-receptor-mediated biological processes. The following examples are designed to provide proof of this therapeutic concept.

##### A. *In vitro* cell-free assay

To demonstrate the inhibitory effects of neuropilin-1-Fc and neuropilin-2-Fc against VEGF-C stimulation, a label, e.g. a biotin molecule, is fused with the VEGF-C protein and first incubated with neuropilin-1-Fc, neuropilin-2-Fc, VEGFR-2 Fc or VEGFR-3-Fc at various molar ratios, and then applied on microtiter plates pre-coated with 1 microgram/ml of VEGFR-3 or VEGFR-2. After blocking with 1%BSA/PBS-T, fresh, labeled VEGF-C protein or the VEGF-C/receptor-Fc mixture above is applied on the microtiter plates overnight at 4 degrees Centigrade. Thereafter, the plates are washed with PBS-T, and 1:1000 of avidin-HRP will be added. Bound VEGF-C protein is detected by addition of the ABTS substrate (KPL). The bound labeled VEGF-C is analyzed in the presence and absence of the soluble neuropilins or soluble VEGFRs and the percent inhibition of binding assessed, as well as the effects the neuropilins have on binding to either VEGFR-2 or VEGFR-3 coated microtiter plates. In a related variation, this assay is carried out substituting VEGF-D for VEGF-C.

##### B. *In vitro* cell-based assay

VEGF-C is used as described above to contact cells that naturally or recombinantly express NRP-2 and VEGFR-3 receptors on their surface. By way of example, 293EBNA or 293T cells recombinantly modified to transiently or stably express neuropilins and VEGFR-3 as outlined above are employed. Several native endothelial cell types express both receptors and can also be employed, including but not limited to, human microvascular endothelial cells (HMEC) and human cutaneous fat pad microvascular cells (HUVEC).

For assessment of autophosphorylation of VEGFR-3, 293T or 293EBNA human embryonic kidney cells grown in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal calf serum (GIBCO BRL), glutamine

and antibiotics, are transfected using the FUGENETM 6 transfection reagent (Roche Molecular Biochemicals) with plasmid DNAs encoding the receptor constructs ( VEGFR-3 or VEGFR-3-myc tag and/or neuropilin-V5 tag,) or an empty pcDNA3.1z+ vector (Invitrogen). For stimulation assay, the 293EBNA cell monolayers are starved  
5 overnight (36 hours after transfection) in serum-free medium containing 0.2% BSA. The 293EBNA cells are then stimulated with 300 ng/ml recombinant DNDC VEGF-C (Joukov et al., EMBO J. 16:3898-3911. 1997) for 10 min at +37 °C, in the presence or absence of neuropilin-Fc to determine inhibition of VEGF-C/VEGFR-3 binding. The cells are then washed twice with cold phosphate buffered saline (PBS) containing 2  
10 mM vanadate and 2 mM phenylmethylsulfonyl fluoride (PMSF), and lysed into PLCLB buffer (150 mM NaCl, 5% glycerol, 1% Triton X-100, 1.5 M MgCl<sub>2</sub>, and 50 mM Hepes, pH 7.5) containing 2 mM Vanadate, 2 mM PMSF, 0.07 U/ml Aprotinin, and 4 mg/ml leupeptin. The lysates are centrifuged for 10 min at 19 000 g, and incubated with the superantants for 2 h on ice with 2 µg/ml of monoclonal anti-  
15 VEGFR-3 antibodies (9D9f9) (Jussila et al., Cancer Res. 58:1599-1604. 1998), or alternatively with antibodies against the specific tag epitopes (1.1 mg/ml of anti-V5 antibodies (Invitrogen) or 5 µg/ml anti-Myc antibodies (BabCO). The immunocomplexes are incubated with protein A sepharose (Pharmacia) for 45 min with rotation at +4 °C and the sepharose beads washed three times with cold PLCLB  
20 buffer (2 mM vanadate, 2 mM PMSF). The bound polypeptides are separated by 7.5% SDS-PAGE and transferred to a Protran nitrocellulose filter (Schleicher & Schuell) using semi-dry transfer apparatus. After blocking with 5% BSA in TBS-T buffer (10 mM Tris pH 7.5, 150 mM NaCl, 0.1% Tween 20), the filters are stained with the phosphotyrosine-specific primary antibodies (Upstate Biotechnology), followed by  
25 biotinylated goat-anti-mouse immunoglobulins (Dako) and Biotin-Streptavidin HRP complex (Amersham) Phosphotyrosine-specific bands are visualized by enhanced chemiluminescence (ECL). To analyze the samples for the presence of VEGFR-3, the filters are stripped for 30 min at +55 °C in 100 mM 2-mercaptoethanol, 2% SDS, 62.5 mM Tris-HCl pH 6.7 with occasional agitation, and stained with 9D9f9 antibodies  
30 and HRP conjugated rabbit-anti-mouse immunoglobulins (Dako) for antigen detection. Reduced VEGFR-3 autophosphorylation is indicative of successful neuropilin-Fc-mediated inhibition of VEGF-C/VEGFR3 binding.

VEGF-C protein naturally secreted into media conditioned by a PC-3 prostatic adenocarcinoma cell line (ATCC CRL 1435) in serum-free Ham's F-12 Nutrient mixture (GIBCO) (containing 7% fetal calf serum (FCS)) (U.S. Patent 6,221,839) can be used to activate VEGFR3 expressing cells in vitro. For in vitro assay purposes, cells can be reseeded and grown in this medium, which is subsequently changed to serum-free medium. As shown in a previous experiment, pretreatment of the concentrated PC-3 conditioned medium with 50 microliters of VEGFR-3 extracellular domain coupled to CNBr-activated sepharose CL-4B (Pharmacia; about 1 mg of VEGFR-3EC domain/ml sepharose resin) completely abolished VEGFR-3 tyrosine phosphorylation (U.S. Patent 6,221,839). In a related experiment, the PC-3 conditioned media can be pre-treated with a neuropilin composition or control Fc coupled to sepharose. The cells can be lysed, immunoprecipitated using anti-VEGFR-3 antiserum, and analyzed by Western blot using anti-phosphotyrosine antibodies as previously described. The percent inhibition of VEGF-C binding and downstream VEGFR-3 autophosphorylation as a result of neuropilin sequestering of VEGF-C can be determined in this more biologically relevant situation.

The above experiments will also be carried out with relevant semaphorin proteins in conjunction with the neuropilin composition of the invention to determine the effects of another natural ligand for the neuropilin receptor on blocking VEGF-C/neuropilin receptor interactions. If the VEGF-C and semaphorin bind neuropilins in the same site on the receptor, there will be a subsequent increase in VEGF-C binding to VEGFR-3 and VEGFR-3 phosphorylation, due to the increase in VEGF-C unbound to the neuropilin-Fc. However, if the semaphorins and VEGF-C bind at different sites on the neuropilin receptor and do not inhibit each other's binding, then the amount of VEGF-C binding to VEGFR-3 will be comparable to binding in the absence of the semaphorins, i.e. with neuropilin-Fc alone. This assay will further define VEGF-C/neuropilin interactions.

The aforementioned in vitro cell-free and cell-based assays can also be performed with putative modulator compounds, eg cytokines that affect VEGF-C secretion ( TNF $\alpha$ , TGF $\beta$ , PDGF, TGF $\alpha$ , FGF-4, EGF, IL-1 $\alpha$  IL-1 $\beta$ , IL-6) to determine the efficacy of the neuropilin composition at blocking VEGF-C activity in the presence of VEGF-C modulators which are biologically active in situations of



inflammation and tumor growth, comparing the neuropilin composition to current experimental cancer therapeutics.

#### EXAMPLE 4

#### 5      **EFFECTS OF NEURPILIN-2/VEGF-C BINDING ON VEGF-C RELATED BIOLOGICAL FUNCTIONS**

VEGF-C is intimately involved with many functions of lymphangiogenesis and endothelial cell growth. The influence of NRP-2 on such VEGF-C functions in vivo is investigated using the following assays:

##### 10      A.      Cell migration assay

For example, human microvascular endothelial cells (HMVEC) express VEGFR-3 and NRP-2, and such cells can be used to investigate the effect of soluble and membrane bound neuropilin receptors on such cells. Since neuropilins and VEGF/VEGFR interactions are thought to play a role in migration of cells, a cell  
15 migration assay using HMVEC or other suitable cells can be used to demonstrate stimulatory or inhibitory effects of neuropilin molecules.

Using a modified Boyden chamber assay, polycarbonate filter wells (Transwell, Costar, 8 micrometer pore) are coated with 50 micrograms/ml fibronectin (Sigma), 0.1% gelatin in PBS for 30 minutes at room temperature, followed by  
20 equilibration into DMEM/0.1% BSA at 37 degrees C for 1 hour. HMVEC (passage 4-9,  $1 \times 10^5$  cells) naturally expressing VEGFR-3 and neuropilin receptors or endothelial cell lines recombinantly expressing VEGFR-3 and/or NRP-2 are plated in the upper chamber of the filter well and allowed to migrate to the undersides of the filters, toward the bottom chamber of the well, which contains serum-free media  
25 supplemented with prepro-VEGF-C, or enzymatically processed VEGF-C, in the presence of varying concentrations of neuropilin-1-Fc, neuropilin-2-Fc, and VEGFR-3-Fc protein. After 5 hours, cells adhering to the top of the transwell are removed with a cotton swab, and the cells that migrate to the underside of the filter are fixed and stained. For quantification of cell numbers, 6 randomly selected 400X  
30 microscope fields are counted per filter.

In another variation, the migration assay described above is carried out using porcine aortic endothelial cells (PAEC) stably transfected with constructs such as those described previously, to express NRP-2, VEGFR-3, or both NRP-2 and

VEGFR-3 (i.e. PAE/NRP-2, PAE/VEGFR-3, or PAE/NRP-2/VEGFR-3). PAEC are transfected using the method described in Soker et al. (Cell 92:735-745, 1998).

Transfected PAEC ( $1.5 \times 10^4$  cells in serum free F12 media supplemented with 0.1% BSA) are plated in the upper wells of a Boyden chamber prepared with fibronectin as described above. Increasing concentrations of VEGF-C or VEGF-D are added to the wells of the lower chamber to induce migration of the endothelial cells. After 4hrs, the number of cells migrating through the filter is quantitated by phase microscopy.

An increase in migration and chemotaxis of NRP-2/VEGFR-3 double transfectants over NRP-2 or VEGFR-3 single transfectants indicates that the presence of neuropilin-2 enhances the ability of VEGF-C or VEGF-D to signal through VEGFR-3 and stimulate downstream biological effects, particularly cell migration and, likely, angiogenesis or lymphangiogenesis.

Additionally, the porcine aortic endothelial cell migration assay is used to identify modulators of NRP-2/VEGFR-3/VEGF-C mediated stimulation of endothelial cells. Migration of PAE/NRP-2/VEGFR-3 expressing cells is assessed after the addition of compositions, such as soluble receptor peptides, proteins or other small molecules (e.g. monoclonal and bispecific antibodies or chemical compounds), to the lower wells of the Boyden chamber in combination with VEGF-C ligand. A decrease in migration as a result of the addition of any of the peptides, proteins or small molecules identifies that composition as an inhibitor of NRP-2/VEGFR-3 mediated chemotaxis.

#### B. Mitogen assay

Embryonic endothelial cells expressing VEGFR-3 alone, NRP-2 alone, or both VEGFR-3 and NRP-2 are cultured in the presence or absence of VEGF-C polypeptides, and potential modulators of this interactions such as semaphorins, more particularly Sema3F, as well as cytokines which may include but are not limited to TGF- $\beta$ , TNF- $\alpha$ , IL-1 $\alpha$  and IL-1 $\beta$ , IL-6, and PDGF, known to upregulate VEGF-C activity, to assay effects on cell growth using any cell growth or migration assay, such as assays that measure increase in cell number or assays that measure tritiated thymidine incorporation. See, e.g., Thompson et al., Am. J. Physiol. Heart Circ. Physiol., 281: H396-403 (2001).

## EXAMPLE 5 ANGIOGENESIS ASSAYS

There continues to be a long-felt need for additional agents that can stimulate angiogenesis, e.g., to promote wound healing, or to promote successful tissue grafting and transplantation, as well as agents to inhibit angiogenesis (e.g., to inhibit growth of tumors). Moreover, various angiogenesis stimulators and inhibitors may work in concert through the same or different receptors, and on different portions of the circulatory system (e.g., arterieries or veins or capillaries; vascular or lymphatic). Angiogenesis assays are employed to measure the effects of neuropilin/VEGF-C interactions, on angiogenic processes, alone or in combination with other angiogenic and anti-angiogenic factors to determine preferred combination therapy involving neuropilins and other modulators. Exemplary procedures include the following.

### A. *In vitro* assays for angiogenesis

#### 1. Sprouting assay

HMVEC cells (passage 5-9) are grown to confluency on collagen coated beads (Pharmacia) for 5-7 days. The beads are plated in a gel matrix containing 5.5 mg/ml fibronectin (Sigma), 2 units/ml thrombin (Sigma), DMEM/2% fetal bovine serum (FBS) and the following test and control proteins: 20 ng/ml VEGF, 20 ng/ml VEGF-C, or growth factors plus 10 micrograms/ml neuropilin-2-Fc, and several combinations of angiogenic factors and Fc fusion proteins. Serum free media supplemented with test and control proteins is added to the gel matrix every 2 days and the number of endothelial cell sprouts exceeding bead length are counted and evaluated.

#### 2. Migration assay

The transwell migration assay previously described may also be used in conjunction with the sprouting assay to determine the effects the neuropilin compositions of the invention have on the interactions of VEGF-C activators and cellular function. The effects of VEGF-Cs on cellular migration are assayed in response the neuropilin compositions of the invention, or in combination with known angiogenic or anti-angiogenic agents. A decrease in cellular migration due to the presence of the neuropilins after VEGF-C stimulation indicates that the invention provides a method for inhibiting angiogenesis.

This assay may also be carried out with cells that naturally express either VEGFR-3 or VEGFR-2, e.g. bovine endothelial cells which preferentially express VEGFR-2. Use of naturally occurring or transiently expressing cells displaying a specific receptor may determine that the neuropilin composition of the invention may be used to preferentially treat diseases involving aberrant activity of either VEGFR-3 or VEGFR-2.

B. *In vivo* assays for angiogenesis

1. Chorioallantoic Membrane (CAM) assay

Three-day old fertilized white Leghorn eggs are cracked, and chicken embryos with intact yolks are carefully placed in 20x100 mm plastic Petri dishes. After six days of incubation in 3% CO<sub>2</sub> at 37 degrees C, a disk of methylcellulose containing VEGF-C and various combinations of the neuropilin compositions, VEGFR-3, and neuropilin-2 and VEGFR-3 complexes, dried on a nylon mesh (3x3mm) is implanted on the CAM of individual embryos, to determine the influence of neuropilins on vascular development and potential uses thereof to promote or inhibit vascular formation. The nylon mesh disks are made by desiccation of 10 microliters of 0.45% methylcellulose (in H<sub>2</sub>O). After 4-5 days of incubation, embryos and CAMs are examined for the formation of new blood vessels and lymphatic vessels in the field of the implanted disks by a stereoscope. Disks of methylcellulose containing PBS are used as negative controls. Antibodies that recognize both blood and lymphatic vessel cell surface molecules are used to further characterize the vessels.

2. Corneal assay

Corneal micropockets are created with a modified von Graefe cataract knife in both eyes of male 5- to 6-week-old C57BL6/J mice. A micropellet (0.35 x 0.35 mm) of sucrose aluminum sulfate (Bukh Meditec, Copenhagen, Denmark) coated with hydron polymer type NCC (IFN Science, New Brunswick, NJ) containing various concentrations of VEGF molecules (especially VEGF-C or VEGF-D) alone or in combination with: i) factors known to modulate vessel growth (e.g., 160 ng of VEGF, or 80 ng of FGF-2) ; ii) neuropilin polypeptides outlined above; or iii) neuropilin polypeptides in conjunction with natural neuropilin ligands such as semaphorins, e.g. Sema-3C and Sema3F, is implanted into each pocket. The pellet is positioned 0.6-0.8 mm from the limbus. After implantation, erythromycin /ophthalmic ointment is applied to the eyes. Eyes are examined by a slit-lamp biomicroscope over

a course of 3-12 days. Vessel length and clock-hours of circumferential neovascularization and lymphangiogenesis are measured. Furthermore, eyes are cut into sections and are immunostained for blood vessel and/or lymphatic markers (LYVE-1 [Prevo et al., J. Biol. Chem., 276: 19420-19430 (2001)], podoplanin [Breiteneder-Geleff et al., Am. J. Pathol., 154: 385-94 (1999).] and VEGFR-3) to further characterize affected vessels.

## EXAMPLE 6 IN VIVO TUMOR MODELS

There is mounting evidence that neuropilin receptors may play a significant role in tumor progression. Neuropilin-1 receptors are found in several tumor cell lines and transfection of NRP-1 into AT2.1 cells can promote tumor growth and vascularization (Miao et al, FASEB J. 14: 2532-39. 2000). Additionally, investigation of neuropilin-2 expression in carcinoid tumors, slowly developing tumors derived from neuroendocrine cells in the digestive tract, illustrates that neuropilin-2 is actually expressed in normal tissue surrounding the tumor, but not in the center of the tumor itself (Cohen et al, Biochem. Biophys. Res. Comm. 284: 395-403. 2001), and it is established that neuroendocrine cells secrete VEGF-C, VEGF-D, and express VEGFR-3 on their cell surface (Partanen, et al., FASEB J 14:2087-96. 2000). Differential expression levels of these neuropilins in association with VEGF molecules, which are often correlative with vascular density and tumor progression, in and around tumors could be indicative of tumor progression or regression.

### A. Ectopic Tumor Implantation

Six- to 8-week-old nude (nu/nu) mice (SLC, Shizuoka, Japan) undergo subcutaneous transplantation of C6 rat glioblastoma cells or PC-3 prostate cancer cells in 0.1 mL phosphate-buffered saline (PBS) on the right flank. The neuropilin polypeptides outlined previously are administered to the animals at various concentrations and dosing regimens. Tumor size is measured in 2 dimensions, and tumor volume is calculated using the formula, width<sup>2</sup> x length/2. After 14 days, the mice are humanely killed and autopsied to evaluate the quantity and physiology of tumor vasculature in response to VEGF-C inhibition by neuropilin polypeptides.

It will be apparent that the assay can also be performed using other tumor cell lines implanted in nude mice or other mouse strains. Use of wild type mice

implanted with LLC lung cancer cells and B16 melanoma cells is specifically contemplated.

**B Orthotopic tumor implantation**

Approximately  $1 \times 10^7$  MCF-7 breast cancer cells in PBS are  
5 inoculated into the fat pads of the second (axillar) mammary gland of ovariectomized SCID mice or nude mice, carrying s.c. 60-day slow-release pellets containing 0.72 mg of 17 $\beta$ -estradiol (Innovative Research of America). The ovariectomy and implantation of the pellets are done 4-8 days before tumor cell inoculation. The neuropilin polypeptides and VEGF-C polypeptides outlined previously, as well as semaphorins,  
10 specifically Sema3C and Sema3F, are administered to the animals at various concentrations and dosing regimens. Tumor size is measured in 2 dimensions, and tumor volume is calculated using the formula, width  $2 \times$  length/2. After 14 days, the mice are humanely killed and autopsied to evaluate the quantity and physiology of tumor vasculature.

15 A similar protocol is employed wherein PC-3 cells are implanted into the prostate of male mice.

**C. Lymphatic metastasis model**

VEGF-C/VEGFR3 interactions are often associated in adult tissue with the organization and growth of lymphatic vessels, thus the presence of neuropilin  
20 receptor at these sites may be involved in the metastatic nature of some cancers. The following protocol indicates the ability of neuropilin polypeptides, especially neuropilin-2 polypeptides, or fragments thereof for inhibition of lymphatic metastasis.

MDA-MB-435 breast cancer cells are injected bilaterally into the second mammary fat pads of athymic, female, eight week old nude mice. The cells  
25 often metastasize to lymph node by 12 weeks. Initially, the role of neuropilin-2 binding to VEGF-C and VEGFR-3 in tumor metastasis can be assessed using modulators of neuropilin-VEGF-C binding determined previously, especially contemplated are the semaphorins. A decrease in metastasis correlating with NRP-2 blockade indicates NRP-2 is critical in tumor metastasis. The modulators of  
30 neuropilin-VEGF-C binding determined previously [by the invention] are then administered to the animals at various concentrations and dosing regimens. Moreover, the neuropilin-2 polypeptides are administered in combination with other

materials for reducing tumor metastasis. See, e.g., International Patent Publication No. WO 00/21560, incorporated herein by reference in its entirety. Mice are sacrificed after 12 weeks and lymph nodes are investigated by histologic analysis. Decrease in lymphatic vessels and tumor spread as a result of administration of the  
5 neuropilin compositions indicate the invention may be a therapeutic compound in the prevention of tumor metastasis.

#### EXAMPLE 7 ASSESSMENT OF VEGF-C ON GROWTH CONE COLLAPSE BY 10 COLLAGEN REPULSION ASSAY

The constitutive expression of semaphorins in the central nervous system has been proposed as a primary factor in the lack of regeneration of nerves in this area. Regeneration of peripheral nerves after nerve insult, such as sciatic nerve crush, is made possible by the downregulation of semaphorin-3A expression  
15 immediately following injury. Sema3A expression returns to baseline levels after approximately 36 days following injury, but this extended period of decreased semaphorin expression allows for the growth and regeneration of the peripheral nerve into the area of damage before the regrowth is halted by semaphorin activity (reviewed in Pasterkamp and Verhaagen, Brain Res. Rev. 35: 36-54. 2000). While  
20 numerous semaphorins are extensively expressed in the CNS and PNS, semaphorin-3F, the primary ligand for neuropilin-2, demonstrates wide distribution in human brain, and has even been found to be overexpressed in certain areas of the brain in Alzheimer's patients (Hirsch et al, Brain Res. 823:67-79. 1999). The newly  
25 discovered interaction of VEGF-C binding to NRP-2 may provide a factor for specifically inhibiting the actions of sema-3F activity in halting neural regeneration in many neurodegenerative diseases such as Alzheimer's or macular degeneration.

Superior cervical ganglia (SCG) are dissected out of E13.5 or E15.5-17.5 rat or mouse embryos according to the method of Chen et al (Neuron, 25:43-56. 2000) and Giger et al (Neuron, 25:29-41. 2000) for use in a collagen repulsion assay.  
30 Following dissection, hindbrain-midbrain junction explants are co-cultured with COS cells recombinantly modified to express Alkaline phosphatase conjugated Sema3F or mock transfected COS cells in collagen matrices in culture medium [OPTI-MEM and F12 at 70:25, supplemented with 1% P/S, Glutamax (Gibco), 5% FCS and 40mM

glucose] for 48h. Neurite extension is quantitated using the protocol outlined by Giger et al (Neuron, 25:29-41. 2000), briefly described by determining the percentage of neurite extension beyond a defined point in the culture matrix. Neurite extension can be measured in the presence of varying concentrations of a VEGF-C composition as compared to in the absence of a VEGF-C composition and the subsequent increase of neurite extension as a result of VEGF-C addition to the culture and blockade of  
5       Sema3F interaction with neuropilin-2 can be assessed.

The effects of Sema3F inhibition as a result of the present invention may be extrapolated into treatments for several diseases wherein neuronal  
10       regeneration is prohibited by the presence of semaphorins, for example scarring after cranial nerve damage, and perhaps in the brains of Alzheimer's patients.

Variations to the examples given above will be apparent and are considered aspects of the invention within the claims.

For example, the materials and methods described in the preceding  
15       Examples are useful and readily adapted for screening for new modulators of the polypeptide interactions described herein, and for demonstrating the effects of such new modulators in cell-based systems and in vivo. In other words, the procedures in the materials and methods of the Examples are useful for identifying modulators and screening the modulators for activity in vitro and in vivo.

By way of illustration, Example 1 describes an experimental protocol wherein VEGF-C binding to neuropilins was investigated. Similar binding experiments can be performed in which a test agent is added to the binding experiment at one or more test agent concentrations, to determine if the test agent modulates (increases or decreases) the measurable binding between VEGF-C and the  
20       neuropilin. Example 2 describes an experimental protocol wherein VEGFR-3 binding to neuropilins was investigated. Similar binding experiments can be performed in which a test agent is included in the reaction to determine if the test agent modulates (increases or decreases) the measurable binding between VEGFR-3 and the  
25       neuropilin. Test agents that are identified as modulators in initial binding assays can  
30       be included in cell-based and in vivo assays that are provided in subsequent Examples, to measure the biological effects of the test agents on cells that express



receptors of interest (e.g., VEGFR-3 or neuropilin-expressing cells) or on biological systems and organisms.

Similarly, a number of the Examples describe using a soluble form of neuropilin receptor or other protein in experiments that further prove binding relationships between molecules described herein for the first time. These experiments also demonstrate that molecules that bind one or both members of a ligand/receptor pair or receptor/co-receptor pair can be added to a system to modulate (especially inhibit) the ability of the binding pair to interact. For example, soluble NRP molecules are used in Example 3 to modulate (inhibit) VEGF-C or VEGF-D binding to VEGFR-3 or VEGFR-2. The disruption of VEGF-C or VEGF-D binding to their respective VEGFR receptors has practical applications for treatment of numerous diseases characterized by undesirable ligand-mediated stimulation of VEGFR-3 or VEGFR-2. Similar binding experiments can be performed in which a test agent suspected of modulating the same binding reactions is substituted for the soluble NRP molecule. In this way, the materials and methods of the Examples are used to identify and verify the therapeutic value of test agents.

Practicing the Examples using small organic or inorganic molecules, peptide libraries, and chemical compound libraries in place of the neuropilin or VEGF-C polypeptides is particularly contemplated. Small molecules and chemical compounds identified by the invention as modulators of neuropilin-VEGF-C and/or neuropilin/VEGFR-3 interactions will be useful as therapeutic compositions to treat situations of aberrant neuropilin-VEGF-C interactions, and in the manufacture of a medicament for the treatment of diseases characterized by aberrant growth, migration, or proliferation of cells mediated by VEGF-C binding to NRP-2/ VEGFR-3 complexes.

The foregoing describes and exemplifies the invention but is not intended to limit the invention defined by the claims which follow.

## CLAIMS

What is claimed is:

1. A method of screening for modulators of binding between a neuropilin growth factor receptor and a VEGF-C polypeptide comprising steps of:
  - a) contacting a neuropilin composition that comprises a neuropilin polypeptide with a VEGF-C composition that comprises a VEGF-C polypeptide, in the presence and in the absence of a putative modulator compound;
  - b) detecting binding between the neuropilin polypeptide and the VEGF-C polypeptide in the presence and absence of the putative modulator compound; and
  - c) identifying a modulator compound based on a decrease or increase in binding between the neuropilin polypeptide and the VEGF-C polypeptide in the presence of the putative modulator compound, as compared to binding in the absence of the putative modulator compound.
2. A method according to claim 1, further comprising a step of:
  - (d) making a modulator composition by formulating a modulator identified according to step (c) in a pharmaceutically acceptable carrier.
3. A method according to claim 2, further comprising a step of:
  - (e) administering the modulator composition to an animal that comprises cells that express the neuropilin receptor, and determining physiological effects of the modulator composition in the animal.
4. A method according to any one of claims 1-3 wherein the neuropilin receptor composition comprises a member selected from the group consisting of:
  - (a) a purified polypeptide comprising a neuropilin receptor extracellular domain that binds VEGF-C;
  - (b) a phospholipid membrane containing neuropilin polypeptides; and
  - (c) a cell recombinantly modified to express increased levels of neuropilin receptor polypeptide on the cell surface.

5. A method according to any one of claims 1-3, wherein the neuropilin receptor composition comprises a polypeptide comprising a neuropilin receptor extracellular domain fragment bound to a solid support.
6. A method according to claim 1, wherein the neuropilin receptor composition comprises a polypeptide comprising a neuropilin receptor extracellular domain fragment fused to an immunoglobulin Fc fragment.
7. A method according to any one of claims 1-6, wherein the neuropilin composition comprises a mammalian neuropilin-2 polypeptide .
8. A method according to claim 7, wherein the neuropilin-2 polypeptide is human.
9. A method according to any one of claims 1-6, wherein the neuropilin composition comprises a mammalian neuropilin-1 polypeptide.
10. A method according to claim 1 wherein the VEGF-C composition comprises a purified mammalian prepro-VEGF-C polypeptide or a fragment of the prepro-VEGF-C polypeptide, that binds the neuropilin receptor.
11. A method according to claim 10, wherein the prepro-VEGF-C polypeptide is human.
12. A method according to claim 10, wherein the VEGF-C composition comprises a fragment of human prepro-VEGFC that contains amino acids 103-227 of SEQ ID NO: 24.

13. A method according to any one of claims 10-12, wherein the VEGF-C composition comprises amino acids 32 to 227 of the human prepro-VEGF-C sequence of SEQ. ID. NO: 24.

14. A method according to claim 1, wherein the VEGF-C composition comprises a conditioned media from a cell recombinantly modified to express and secrete a VEGF-C polypeptide.

15. A method according to any one of claims 1-3, wherein the neuropilin composition comprises a cell recombinantly modified to express increased amounts of a neuropilin receptor on its surface, and wherein the detecting step comprises measuring a VEGF-C binding-induced physiological change in the cell.

16. A method for screening for selectivity of a modulator of VEGF-C biological activity, comprising steps of:

a) contacting a VEGF-C composition with a neuropilin composition in the presence and in the absence of a compound and detecting binding between the VEGF-C and the neuropilin in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the VEGF-C and the neuropilin;

b) contacting a VEGF-C composition with a composition comprising a VEGF-C binding partner in the presence and in the absence of the compound and detecting binding between the VEGF-C and the binding partner in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the VEGF-C and the binding partner; and wherein the binding partner is selected from the group consisting of:

- (i) a polypeptide comprising a VEGFR-3 extracellular domain; and
- (ii) a polypeptide comprising a VEGFR-2 extracellular domain; and
- (c) identifying the selectivity of the modulator compound in view of the binding detected in steps (a) and (b).

17. A method for screening for selectivity of a modulator of neuropilin biological activity, comprising steps of:

a) contacting a neuropilin composition with a VEGF-C composition in the presence and in the absence of a compound and detecting binding between the neuropilin and the VEGF-C in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the neuropilin and the VEGF-C;

b) contacting a neuropilin composition with a composition comprising a neuropilin binding partner in the presence and in the absence of the compound and detecting binding between the neuropilin and the binding partner in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the neuropilin and the binding partner; and wherein the binding partner is a polypeptide comprising an amino acid sequence selected from the group consisting of:

an amino acid sequence of a semaphorin 3 polypeptide; a VEGF-A amino acid sequence, a VEGF-B amino acid sequence, a VEGF-D amino acid sequence, a PlGF-2 amino acid sequence, a VEGFR-1 amino acid sequence, a VEGFR-2 amino acid sequence, a VEGFR-3 amino acid sequence; and an amino acid sequence of a plexin polypeptide; and

c) identifying the selectivity of the modulator compound in view of the binding detected in steps (a) and (b).

18. A method according to claim 17 wherein the binding partner is a human semaphorin.

19. A method of screening for modulators of binding between a neuropilin growth factor receptor and a VEGFR-3 polypeptide comprising steps of:

a) contacting a neuropilin composition with a VEGFR-3 composition in the presence and in the absence of a putative modulator compound;

b) detecting binding between the neuropilin and the VEGFR-3 in the presence and absence of the putative modulator compound; and

c) identifying a modulator compound based on a decrease or increase in binding between the neuropilin composition and the VEGFR-3 composition in the presence of the putative modulator compound, as compared to binding in the absence of the putative modulator compound.

20. A method according to claim 19 wherein the VEGFR-3 composition comprises a member selected from the group consisting of:

(a) a purified polypeptide comprising a VEGFR-3 receptor extracellular domain that binds VEGF-C;

(b) a phospholipid membrane containing VEGFR-3 polypeptides; and

(c) a cell recombinantly modified to express increased levels of VEGFR-3 receptor on the cell surface.

21. A method according to claim 19, wherein the VEGFR-3 composition comprises a VEGFR-3 extracellular domain fragment bound to a solid support.

22. A method according to claim 19, wherein the VEGFR-3 composition comprises a VEGFR-3 extracellular domain fragment fused to an immunoglobulin Fc fragment.

23. A method according to any one of claims 19-22, wherein the VEGFR-3 is a mammalian VEGFR-3.

24. A method according to claim 23, wherein the VEGFR-3 is human.

25. A method for screening for selectivity of a modulator of VEGFR-3 biological activity, comprising steps of:

a) contacting a VEGFR-3 composition with a neuropilin composition in the presence and in the absence of a compound and detecting binding between the VEGFR-3 and the neuropilin in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the VEGFR-3 and the neuropilin;

b) contacting a VEGFR-3 composition with a composition comprising a VEGFR-3 binding partner in the presence and in the absence of the compound and detecting binding between the VEGFR-3 and the binding partner in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the VEGFR-3 and the binding partner; and wherein the binding partner is selected from the group consisting of:

(i) a polypeptide comprising a VEGF-C polypeptide; and

(ii) a polypeptide comprising a VEGF-D polypeptide; and

c) identifying the selectivity of the modulator compound in view of the binding detected in steps (a) and (b).

26. A method of modulating growth, migration, or proliferation of cells in a mammalian organism, comprising a step of:

(a) identifying a mammalian organism having cells that express a neuropilin receptor; and

(b) administering to said mammalian organism a composition, said composition comprising a neuropilin polypeptide or fragment thereof that binds to the VEGF-C polypeptide;

wherein the composition is administered in an amount effective to modulate growth, migration, or proliferation of cells that express neuropilin in the mammalian organism.

27. A method according to claim 26, wherein the mammalian organism is human.

28. A method according to claim 23, further comprising administering a second agent to the patient for modulating endothelial growth, migration, or proliferation through a neuropilin receptor, said second agent comprising a polypeptide comprising an amino acid sequence selected from the group consisting of: a VEGF-A amino acid sequence, a VEGF-B amino acid sequence, a VEGF-D amino acid sequence, a VEGF-E amino acid sequence, a PlGF amino acid sequence, a semaphorin 3A amino acid sequence, semaphorin 3C amino acid sequence, and a semaphorin 3F amino acid sequence.

29. A method of modulating growth, migration, or proliferation of cells in a mammalian organism, comprising steps of:

(a) identifying a mammalian organism having cells that express a neuropilin receptor; and

(b) administering to said mammalian organism a composition, said composition comprising a bispecific antibody specific for the neuropilin receptor and for a VEGF-C polypeptide,

wherein the composition is administered in an amount effective to modulate growth, migration, or proliferation of cells that express the neuropilin receptor in the mammalian organism.

30. A bispecific antibody which specifically binds to a neuropilin receptor and a VEGF-C polypeptide.



31. A method of modulating growth, migration, or proliferation of cells in a mammalian organism, comprising steps of:

- (a) identifying a mammalian organism having cells that express a neuropilin receptor and a VEGFR-3 polypeptide; and
- (b) administering to said mammalian organism a composition, said composition comprising a bispecific antibody specific for the neuropilin receptor and a VEGFR-3 polypeptide,

wherein the composition is administered in an amount effective to modulate growth, migration, or proliferation of cells that express the neuropilin receptor and the VEGFR-3 polypeptide in the mammalian organism.

32. A bispecific antibody which specifically binds to a neuropilin receptor and a VEGFR-3 polypeptide.

33. A method of modulating neuronal growth, or neuronal scarring in a mammalian organism, comprising a step of:

- (a) identifying a mammalian organism having cells that express a neuropilin receptor; and
- (b) administering to said mammalian organism a composition, said composition comprising a VEGF-C polypeptide or fragment thereof that binds to the neuropilin receptor.

34. A method according to claim 33, wherein the mammalian organism is human.

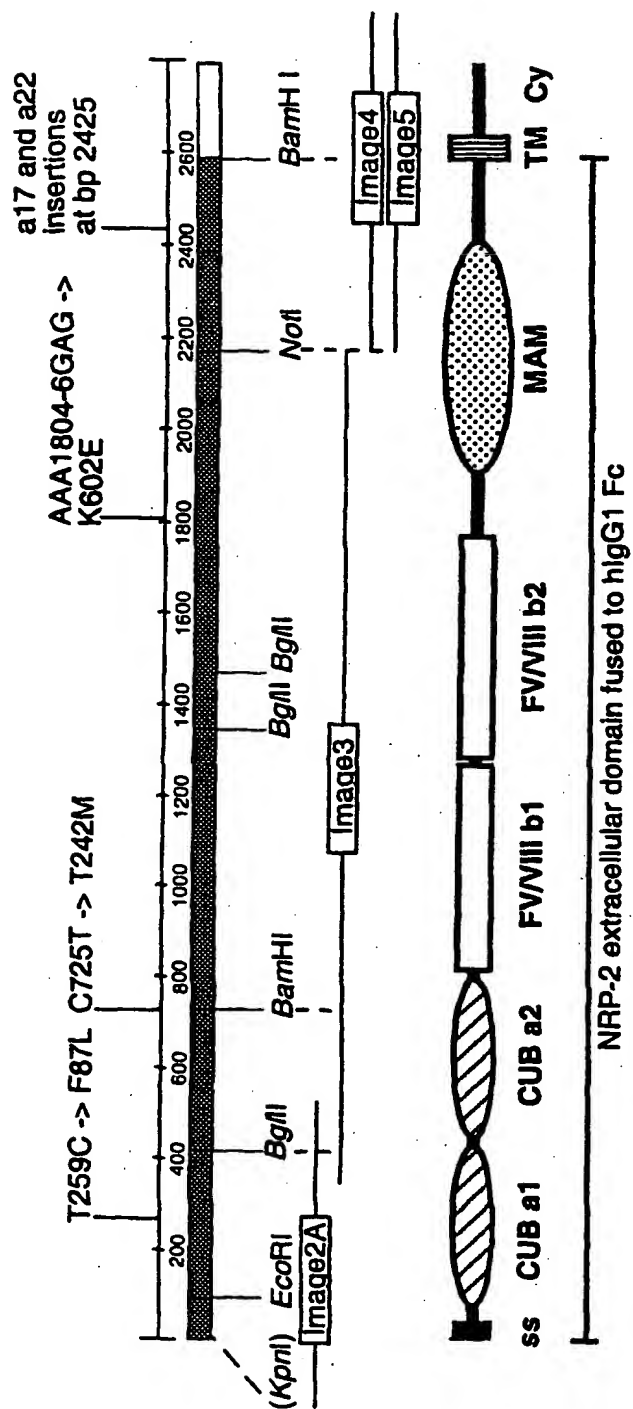
35. A method according to claim 33, wherein the cells comprise neuronal cells that express neuropilin-2.

36. A method according to any one of claims 33, wherein the organism has a disease characterized by aberrant growth of neuronal cells involved in scarring and neural degeneration.

37. A method according to claim 36, wherein the disease comprises a neurodegenerative disorder, more specifically Alzheimer's disease.

38. A polypeptide comprising a fragment of a VEGF-C that binds to a neuropilin receptor, for use in the manufacture of a medicament for the treatment of diseases characterized by aberrant growth, migration, or proliferation of cells that express a neuropilin receptor.

Figure 1.



## SEQUENCE LISTING

<110> Ludwig Institute for Cancer Research et al.

<120> NEUROPILIN/VEGF C/VEGFR 3 MATERIALS AND METHODS

<130> 28967/37564

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<170> PatentIn version 3.0

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625					630					635					640	
tca	gag	ttt	cca	aca	tat	ggg	ttt	aac	tgt	gaa	ttt	ggc	tgg	ggc	tct	1968
Ser	Glu	Phe	Pro	Thr	Tyr	Gly	Phe	Asn	Cys	Glu	Phe	Gly	Trp	Gly	Ser	
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cac	aag	acc	ttc	tgc	cac	tgg	gaa	cat	gac	aat	cac	gtg	cag	ctc	aag	2016
His	Lys	Thr	Phe	Cys	His	Trp	Glu	His	Asp	Asn	His	Val	Gln	Leu	Lys	
			660					665					670			
tgg	agt	gtg	ttg	acc	agc	aag	acg	gga	ccc	att	cag	gat	cac	aca	gga	2064
Trp	Ser	Val	Leu	Thr	Ser	Lys	Thr	Gly	Pro	Ile	Gln	Asp	His	Thr	Gly	
		675					680					685				
gat	ggc	aac	ttc	atc	tat	tcc	caa	gct	gac	gaa	aat	cag	aag	ggc	aaa	2112
Asp	Gly	Asn	Phe	Ile	Tyr	Ser	Gln	Ala	Asp	Glu	Asn	Gln	Lys	Gly	Lys	
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Val	Ala	Arg	Leu	Val	Ser	Pro	Val	Val	Tyr	Ser	Gln	Asn	Ser	Ala	His	
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tgc	atg	acc	ttc	tgg	tat	cac	atg	tct	ggg	tcc	cac	gtc	ggc	aca	ctc	2208
Cys	Met	Thr	Phe	Trp	Tyr	His	Met	Ser	Gly	Ser	His	Val	Gly	Thr	Leu	
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agg	gtc	aaa	ctg	cgc	tac	cag	aag	cca	gag	gag	tac	gat	cag	ctg	gtc	2256
Arg	Val	Lys	Leu	Arg	Tyr	Gln	Lys	Pro	Glu	Glu	Tyr	Asp	Gln	Leu	Val	
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Trp	Met	Ala	Ile	Gly	His	Gln	Gly	Asp	His	Trp	Lys	Glu	Gly	Arg	Val	
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Leu	Leu	His	Lys	Ser	Leu	Lys	Leu	Tyr	Gln	Val	Ile	Phe	Glu	Gly	Glu	
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Asn	Asn	His	Ile	Ser	Gln	Glu	Asp	Cys	Ala	Lys	Pro	Ala	Asp	Leu	Asp	
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Lys	Lys	Asn	Pro	Glu	Ile	Lys	Ile	Asp	Glu	Thr	Gly	Ser	Thr	Pro	Gly	

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Tyr Glu Gly Glu Gly Glu Gly	Asp Lys Asn Ile Ser Arg Lys Pro Gly		
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Asn Val Leu Lys Thr Leu Glu Pro Ile Leu Ile Thr Ile Ile Ala Met			
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agc gcc ctg ggg gtc ctc ctg ggg gct gtc tgt ggg gtc gtg ctg tac			2640
Ser Ala Leu Gly Val Leu Leu Gly Ala Val Cys Gly Val Val Leu Tyr			
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Cys Ala Cys Trp His Asn Gly Met Ser Glu Arg Asn Leu Ser Ala Leu			
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gag aac tat aac ttt gaa ctt gtg gat ggt gtg aag ttg aaa aaa gac			2736
Glu Asn Tyr Asn Phe Glu Leu Val Asp Gly Val Lys Leu Lys Lys Asp			
900	905		910
aaa ctg aat aca cag agt act tat tcg gag gca tga			2772
Lys Leu Asn Thr Gln Ser Thr Tyr Ser Glu Ala			
915	920		

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&lt;211&gt; 923

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 2

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His Pro Ser Glu Lys Cys Glu Trp Leu Ile Gln Ala Pro Asp Pro Tyr	
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Gln Arg Ile Met Ile Asn Phe Asn Pro His Phe Asp Leu Glu Asp Arg	
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Asp Cys Lys Tyr Asp Tyr Val Glu Val Phe Asp Gly Glu Asn Glu Asn	
85 90 95	



Gly His Phe Arg Gly Lys Phe Cys Gly Lys Ile Ala Pro Pro Pro Val  
 100 105 110  
 Val Ser Ser Gly Pro Phe Leu Phe Ile Lys Phe Val Ser Asp Tyr Glu  
 115 120 125  
 Thr His Gly Ala Gly Phe Ser Ile Arg Tyr Glu Ile Phe Lys Arg Gly  
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 Pro Glu Cys Ser Gln Asn Tyr Thr Thr Pro Ser Gly Val Ile Lys Ser  
 145 150 155 160  
 Pro Gly Phe Pro Glu Lys Tyr Pro Asn Ser Leu Glu Cys Thr Tyr Ile  
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 Val Phe Ala Pro Lys Met Ser Glu Ile Ile Leu Glu Phe Glu Ser Phe  
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 Asp Leu Glu Pro Asp Ser Asn Pro Pro Gly Gly Met Phe Cys Arg Tyr  
 195 200 205  
 Asp Arg Leu Glu Ile Trp Asp Gly Phe Pro Asp Val Gly Pro His Ile  
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 225 230 235 240  
 Gly Ile Leu Ser Met Val Phe Tyr Thr Asp Ser Ala Ile Ala Lys Glu  
 245 250 255  
 Gly Phe Ser Ala Asn Tyr Ser Val Leu Gln Ser Ser Val Ser Glu Asp  
 260 265 270  
 Phe Lys Cys Met Glu Ala Leu Gly Met Glu Ser Gly Glu Ile His Ser  
 275 280 285  
 Asp Gln Ile Thr Ala Ser Ser Gln Tyr Ser Thr Asn Trp Ser Ala Glu  
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 Arg Ser Arg Leu Asn Tyr Pro Glu Asn Gly Trp Thr Pro Gly Glu Asp  
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 Ser Tyr Arg Glu Trp Ile Gln Val Asp Leu Gly Leu Leu Arg Phe Val  
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 Thr Ala Val Gly Thr Gln Gly Ala Ile Ser Lys Glu Thr Lys Lys Lys

340

345

350

Tyr Tyr Val Lys Thr Tyr Lys Ile Asp Val Ser Ser Asn Gly Glu Asp  
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Trp Ile Thr Ile Lys Glu Gly Asn Lys Pro Val Leu Phe Gln Gly Asn  
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Thr Asn Pro Thr Asp Val Val Val Ala Val Phe Pro Lys Pro Leu Ile  
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Thr Arg Phe Val Arg Ile Lys Pro Ala Thr Trp Glu Thr Gly Ile Ser  
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Met Arg Phe Glu Val Tyr Gly Cys Lys Ile Thr Asp Tyr Pro Cys Ser  
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Gly Met Leu Gly Met Val Ser Gly Leu Ile Ser Asp Ser Gln Ile Thr  
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Ser Ser Asn Gln Gly Asp Arg Asn Trp Met Pro Glu Asn Ile Arg Leu  
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Val Thr Ser Arg Ser Gly Trp Ala Leu Pro Pro Ala Pro His Ser Tyr  
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Ile Asn Glu Trp Leu Gln Ile Asp Leu Gly Glu Glu Lys Ile Val Arg  
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Gly Ile Ile Ile Gln Gly Gly Lys His Arg Glu Asn Lys Val Phe Met  
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Arg Lys Phe Lys Ile Gly Tyr Ser Asn Asn Gly Ser Asp Trp Lys Met  
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Asn Tyr Asp Thr Pro Glu Leu Arg Thr Phe Pro Ala Leu Ser Thr Arg  
 545 550 555 560

Phe Ile Arg Ile Tyr Pro Glu Arg Ala Thr His Gly Gly Leu Gly Leu  
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Arg Met Glu Leu Leu Gly Cys Glu Val Glu Ala Pro Thr Ala Gly Pro  
 580 585 590

Thr Thr Pro Asn Gly Asn Leu Val Asp Glu Cys Asp Asp Asp Gln Ala  
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 Asn Cys His Ser Gly Thr Gly Asp Asp Phe Gln Leu Thr Gly Gly Thr  
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 Thr Val Leu Ala Thr Glu Lys Pro Thr Val Ile Asp Ser Thr Ile Gln  
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 Ser Glu Phe Pro Thr Tyr Gly Phe Asn Cys Glu Phe Gly Trp Gly Ser  
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 His Lys Thr Phe Cys His Trp Glu His Asp Asn His Val Gln Leu Lys  
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 Trp Ser Val Leu Thr Ser Lys Thr Gly Pro Ile Gln Asp His Thr Gly  
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 Val Ala Arg Leu Val Ser Pro Val Val Tyr Ser Gln Asn Ser Ala His  
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 Cys Met Thr Phe Trp Tyr His Met Ser Gly Ser His Val Gly Thr Leu  
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 Trp Met Ala Ile Gly His Gln Gly Asp His Trp Lys Glu Gly Arg Val  
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 770 775 780  
 Ile Gly Lys Gly Asn Leu Gly Gly Ile Ala Val Asp Asp Ile Ser Ile  
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 Lys Lys Asn Pro Glu Ile Lys Ile Asp Glu Thr Gly Ser Thr Pro Gly  
 820 825 830  
 Tyr Glu Gly Glu Gly Glu Gly Asp Lys Asn Ile Ser Arg Lys Pro Gly  
 835 840 845

Asn Val Leu Lys Thr Leu Glu Pro Ile Leu Ile Thr Ile Ile Ala Met  
 850 855 860

Ser Ala Leu Gly Val Leu Leu Gly Ala Val Cys Gly Val Val Leu Tyr  
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Cys Ala Cys Trp His Asn Gly Met Ser Glu Arg Asn Leu Ser Ala Leu  
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 Arg His Gln Val Arg Gly Gln Pro Asp Pro Pro Cys Gly Gly Arg Leu  
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aat tcc aaa gat gct ggc tat atc acc tct ccc ggt tac ccc cag gac 144  
 Asn Ser Lys Asp Ala Gly Tyr Ile Thr Ser Pro Gly Tyr Pro Gln Asp  
 35 40 45

tac ccc tcc cac cag aac tgc gag tgg att gtt tac gcc ccc gaa ccc 192  
 Tyr Pro Ser His Gln Asn Cys Glu Trp Ile Val Tyr Ala Pro Glu Pro  
 50 55 60

aac cag aag att gtc ctc aac ttc aac cct cac ttt gaa atc gag aag 240  
 Asn Gln Lys Ile Val Leu Asn Phe Asn Pro His Phe Glu Ile Glu Lys  
 65 70 75 80

cac gac tgc aag tat gac ttt atc gag att cgg gat ggg gac agt gaa 288

His	Asp	Cys	Lys	Tyr	Asp	Phe	Ile	Glu	Ile	Arg	Asp	Gly	Asp	Ser	Glu		
				85					90					95			
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Ser	Ala	Asp	Leu	Leu	Gly	Lys	His	Cys	Gly	Asn	Ile	Ala	Pro	Pro	Thr		
			100					105					110				
atc	atc	tcc	tcg	ggc	tcc	atg	ctc	tac	atc	aag	ttc	acc	tcc	gac	tac	384	
Ile	Ile	Ser	Ser	Gly	Ser	Met	Leu	Tyr	Ile	Lys	Phe	Thr	Ser	Asp	Tyr		
		115					120					125					
gcc	cgg	cag	ggg	gca	ggc	ttc	tct	ctg	cgc	tac	gag	atc	ttc	aag	aca	432	
Ala	Arg	Gln	Gly	Ala	Gly	Phe	Ser	Leu	Arg	Tyr	Glu	Ile	Phe	Lys	Thr		
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Gly	Ser	Glu	Asp	Cys	Ser	Lys	Asn	Phe	Thr	Ser	Pro	Asn	Gly	Thr	Ile		
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gaa	tct	cct	ggg	ttt	cct	gag	aag	tat	cca	cac	aac	ttg	gac	tgc	acc	528	
Glu	Ser	Pro	Gly	Phe	Pro	Glu	Lys	Tyr	Pro	His	Asn	Leu	Asp	Cys	Thr		
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ttt	acc	atc	ctg	gcc	aaa	ccc	aag	atg	gag	atc	atc	ctg	cag	ttc	ctg	576	
Phe	Thr	Ile	Leu	Ala	Lys	Pro	Lys	Met	Glu	Ile	Ile	Leu	Gln	Phe	Leu		
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atc	ttt	gac	ctg	gag	cat	gac	cct	ttg	cag	gtg	gga	gag	ggg	gac	tgc	624	
Ile	Phe	Asp	Leu	Glu	His	Asp	Pro	Leu	Gln	Val	Gly	Glu	Gly	Asp	Cys		
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aag	tac	gat	tgg	ctg	gac	atc	tgg	gat	ggc	att	cca	cat	gtt	ggc	ccc	672	
Lys	Tyr	Asp	Trp	Leu	Asp	Ile	Trp	Asp	Gly	Ile	Pro	His	Val	Gly	Pro		
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Leu	Ile	Gly	Lys	Tyr	Cys	Gly	Thr	Lys	Thr	Pro	Ser	Glu	Leu	Arg	Ser		
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tcg	acg	ggg	atc	ctc	tcc	ctg	acc	ttt	cac	acg	gac	atg	gcg	gtg	gcc	768	
Ser	Thr	Gly	Ile	Leu	Ser	Leu	Thr	Phe	His	Thr	Asp	Met	Ala	Val	Ala		
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aag	gat	ggc	ttc	tct	gcg	cgt	tac	tac	ctg	gtc	cac	caa	gag	cca	cta	816	
Lys	Asp	Gly	Phe	Ser	Ala	Arg	Tyr	Tyr	Leu	Val	His	Gln	Glu	Pro	Leu		
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gag	aac	ttt	cag	tgc	aat	gtt	cct	ctg	ggc	atg	gag	tct	ggc	cgg	att	864	
Glu	Asn	Phe	Gln	Cys	Asn	Val	Pro	Leu	Gly	Met	Glu	Ser	Gly	Arg	Ile		
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gct	aat	gaa	cag	atc	agt	gcc	tca	tct	acc	tac	tct	gat	ggg	agg	tgg	912	
Ala	Asn	Glu	Gln	Ile	Ser	Ala	Ser	Ser	Thr	Tyr	Ser	Asp	Gly	Arg	Trp		
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acc	cct	caa	caa	agc	cgg	ctc	cat	ggt	gat	gac	aat	ggc	tgg	acc	ccc	960	
Thr	Pro	Gln	Gln	Ser	Arg	Leu	His	Gly	Asp	Asp	Asn	Gly	Trp	Thr	Pro		
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Asn	Leu	Asp	Ser	Asn	Lys	Glu	Tyr	Leu	Gln	Val	Asp	Leu	Arg	Phe	Leu		
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Thr Met Leu Thr Ala Ile Ala Thr Gln Gly Ala Ile Ser Arg Glu Thr	
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Gln Asn Gly Tyr Tyr Val Lys Ser Tyr Lys Leu Glu Val Ser Thr Asn	
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Gly Glu Asp Trp Met Val Tyr Arg His Gly Lys Asn His Lys Val Phe	
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Gln Ala Asn Asn Asp Ala Thr Glu Val Val Leu Asn Lys Leu His Ala	
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Pro Cys Ser Asn Met Leu Gly Met Leu Ser Gly Leu Ile Ala Asp Ser	
435 440 445	
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Gln Ile Ser Ala Ser Ser Thr Gln Glu Tyr Leu Trp Ser Pro Ser Ala	
450 455 460	
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Ala Arg Leu Val Ser Ser Arg Ser Gly Trp Phe Pro Arg Ile Pro Gln	
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Ala Gln Pro Gly Glu Glu Trp Leu Gln Val Asp Leu Gly Thr Pro Lys	
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Thr Val Lys Gly Val Ile Ile Gln Gly Ala Arg Gly Gly Asp Ser Ile	
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Thr Ala Val Glu Ala Arg Ala Phe Val Arg Lys Phe Lys Val Ser Tyr	
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Ser Leu Asn Gly Lys Asp Trp Glu Tyr Ile Gln Asp Pro Arg Thr Gln	
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Gln Pro Lys Leu Phe Glu Gly Asn Met His Tyr Asp Thr Pro Asp Ile	
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Lys	Ser	Glu	Glu	Thr	Thr	Thr	Pro	Tyr	Pro	Thr	Glu	Glu	Glu	Ala	Thr	
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cct	tcg	gga	ttc	aat	tgc	aac	ttc	gat	ttc	ctc	gag	gag	ccc	tgt	ggc	1968
Pro	Ser	Gly	Phe	Asn	Cys	Asn	Phe	Asp	Phe	Leu	Glu	Glu	Pro	Cys	Gly	
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tgg	atg	tat	gac	cat	gcc	aag	tgg	ctc	cgg	acc	acc	tgg	gcc	agc	agc	2016
Trp	Met	Tyr	Asp	His	Ala	Lys	Trp	Leu	Arg	Thr	Thr	Trp	Ala	Ser	Ser	
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Leu	Gln	Ser	Asp	Ser	Gln	Arg	Glu	Gly	Gln	Tyr	Ala	Arg	Leu	Ile	Ser	
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Pro	Pro	Val	His	Leu	Pro	Arg	Ser	Pro	Val	Cys	Met	Glu	Phe	Gln	Tyr	
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Gln	Ala	Thr	Gly	Gly	Arg	Gly	Val	Ala	Leu	Gln	Val	Val	Arg	Glu	Ala	
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Gln	Ile	Val	Phe	Glu	Gly	Val	Ile	Gly	Lys	Gly	Arg	Ser	Gly	Glu	Ile	
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Ala	Ile	Asp	Asp	Ile	Arg	Ile	Ser	Thr	Asp	Val	Pro	Leu	Glu	Asn	Cys	
	785				790					795					800	
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Met	Glu	Pro	Ile	Ser	Ala	Phe	Ala	Val	Asp	Ile	Pro	Glu	Ile	His	Glu	
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Arg	Glu	Gly	Tyr	Glu	Asp	Glu	Ile	Asp	Asp	Glu	Tyr	Glu	Val	Asp	Trp	

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Ser	Asn	Ser	Ser	Ser	Ala	Thr	Ser	Gly	Ser	Gly	Ala	Pro	Ser	Thr	Asp					
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aaa	gaa	aag	agc	tgg	ctg	tac	acc	ctg	gat	ccc	atc	ctc	atc	acc	atc	2592				
Lys	Glu	Lys	Ser	Trp	Leu	Tyr	Thr	Leu	Asp	Pro	Ile	Leu	Ile	Thr	Ile					
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atc	gcc	atg	agc	tca	ctg	ggc	gtc	ctc	ctg	ggg	gcc	acc	tgt	gca	ggc	2640				
Ile	Ala	Met	Ser	Ser	Leu	Gly	Val	Leu	Leu	Gly	Ala	Thr	Cys	Ala	Gly					
865					870					875					880					
ctc	ctg	ctc	tac	tgc	acc	tgt	tcc	tac	tcg	ggc	ctg	agc	tcc	cga	agc	2688				
Leu	Leu	Leu	Tyr	Cys	Thr	Cys	Ser	Tyr	Ser	Gly	Leu	Ser	Ser	Arg	Ser					
885					890					895										
tgc	acc	aca	ctg	gag	aac	tac	aac	ttc	gag	ctc	tac	gat	ggc	ott	aag	2736				
Cys	Thr	Thr	Leu	Glu	Asn	Tyr	Asn	Phe	Glu	Leu	Tyr	Asp	Gly	Leu	Lys					
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cac	aag	gtc	aag	atg	aac	cac	caa	aag	tgc	tgc	tcc	gag	gca	tga		2781				
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Asn	Ser	Lys	Asp	Ala	Gly	Tyr	Ile	Thr	Ser	Pro	Gly	Tyr	Pro	Gln	Asp					
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Tyr	Pro	Ser	His	Gln	Asn	Cys	Glu	Trp	Ile	Val	Tyr	Ala	Pro	Glu	Pro					
	50					55					60									
Asn	Gln	Lys	Ile	Val	Leu	Asn	Phe	Asn	Pro	His	Phe	Glu	Ile	Glu	Lys					
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His	Asp	Cys	Lys	Tyr	Asp	Phe	Ile	Glu	Ile	Arg	Asp	Gly	Asp	Ser	Glu					
			85						90					95						



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 Ile Ile Ser Ser Gly Ser Met Leu Tyr Ile Lys Phe Thr Ser Asp Tyr  
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 Ala Arg Gln Gly Ala Gly Phe Ser Leu Arg Tyr Glu Ile Phe Lys Thr  
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 Gly Ser Glu Asp Cys Ser Lys Asn Phe Thr Ser Pro Asn Gly Thr Ile  
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 Glu Ser Pro Gly Phe Pro Glu Lys Tyr Pro His Asn Leu Asp Cys Thr  
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 Phe Thr Ile Leu Ala Lys Pro Lys Met Glu Ile Ile Leu Gln Phe Leu  
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 Ile Phe Asp Leu Glu His Asp Pro Leu Gln Val Gly Glu Gly Asp Cys  
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 Lys Tyr Asp Trp Leu Asp Ile Trp Asp Gly Ile Pro His Val Gly Pro  
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 Leu Ile Gly Lys Tyr Cys Gly Thr Lys Thr Pro Ser Glu Leu Arg Ser  
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 Ser Thr Gly Ile Leu Ser Leu Thr Phe His Thr Asp Met Ala Val Ala  
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 Lys Asp Gly Phe Ser Ala Arg Tyr Tyr Leu Val His Gln Glu Pro Leu  
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 Asn Leu Asp Ser Asn Lys Glu Tyr Leu Gln Val Asp Leu Arg Phe Leu  
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 Thr Met Leu Thr Ala Ile Ala Thr Gln Gly Ala Ile Ser Arg Glu Thr  
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Gln Asn Gly Tyr Tyr Val Lys Ser Tyr Lys Leu Glu Val Ser Thr Asn  
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 Gly Glu Asp Trp Met Val Tyr Arg His Gly Lys Asn His Lys Val Phe  
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 Pro Leu Leu Thr Arg Phe Val Arg Ile Arg Pro Gln Thr Trp His Ser  
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 Gln Ile Ser Ala Ser Ser Thr Gln Glu Tyr Leu Trp Ser Pro Ser Ala  
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 Ala Arg Leu Val Ser Ser Arg Ser Gly Trp Phe Pro Arg Ile Pro Gln  
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 Ser Leu Asn Gly Lys Asp Trp Glu Tyr Ile Gln Asp Pro Arg Thr Gln  
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 Gln Pro Lys Leu Phe Glu Gly Asn Met His Tyr Asp Thr Pro Asp Ile  
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 Arg Arg Phe Asp Pro Ile Pro Ala Gln Tyr Val Arg Val Tyr Pro Glu  
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 Arg Trp Ser Pro Ala Gly Ile Gly Met Arg Leu Glu Val Leu Gly Cys  
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 Asp Trp Thr Asp Ser Lys Pro Thr Val Lys Thr Leu Gly Pro Thr Val  
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Lys Ser Glu Glu Thr Thr Thr Pro Tyr Pro Thr Glu Glu Glu Ala Thr  
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 625 630 635 640  
 Pro Ser Gly Phe Asn Cys Asn Phe Asp Phe Leu Glu Glu Pro Cys Gly  
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 Trp Met Tyr Asp His Ala Lys Trp Leu Arg Thr Thr Trp Ala Ser Ser  
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 Pro Pro Val His Leu Pro Arg Ser Pro Val Cys Met Glu Phe Gln Tyr  
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 Arg Glu Gly Tyr Glu Asp Glu Ile Asp Asp Glu Tyr Glu Val Asp Trp  
 820 825 830  
 Ser Asn Ser Ser Ser Ala Thr Ser Gly Ser Gly Ala Pro Ser Thr Asp  
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 Lys Glu Lys Ser Trp Leu Tyr Thr Leu Asp Pro Ile Leu Ile Thr Ile  
 850 855 860

Ile Ala Met Ser Ser Leu Gly Val Leu Leu Gly Ala Thr Cys Ala Gly  
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Leu Leu Leu Tyr Cys Thr Cys Ser Tyr Ser Gly Leu Ser Ser Arg Ser  
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	Met Glu Arg
	1
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5 10 15	

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gag aag tgt gaa tgg cta atc caa gct ccg gaa ccc tac cag aga atc Glu Lys Cys Glu Trp Leu Ile Gln Ala Pro Glu Pro Tyr Gln Arg Ile 55 60 65	548
ata atc aac ttc aac cca cat ttc gat ttg gag gac aga gac tgc aag Ile Ile Asn Phe Asn Pro His Phe Asp Leu Glu Asp Arg Asp Cys Lys 70 75 80	596
tat gac tac gtg gaa gta att gat ggg gag aat gaa ggc ggc cgc ctg Tyr Asp Tyr Val Glu Val Ile Asp Gly Glu Asn Glu Gly Gly Arg Leu 85 90 95	644
tgg ggg aag ttc tgt ggg aag att gca cct tct cct gtg gtg tct tca Trp Gly Lys Phe Cys Gly Lys Ile Ala Pro Ser Pro Val Val Ser Ser 100 105 110 115	692
ggg ccc ttt ctc ttc atc aaa ttt gtc tct gac tat gag aca cat ggg Gly Pro Phe Leu Phe Ile Lys Phe Val Ser Asp Tyr Glu Thr His Gly 120 125 130	740
gca ggg ttt tcc atc cgc tat gaa atc ttc aag aga ggg ccc gaa tgt Ala Gly Phe Ser Ile Arg Tyr Glu Ile Phe Lys Arg Gly Pro Glu Cys 135 140 145	788
tct cag aac tat aca gca cct act gga gtg ata aag tcc cct ggg ttc Ser Gln Asn Tyr Thr Ala Pro Thr Gly Val Ile Lys Ser Pro Gly Phe 150 155 160	836
cct gaa aaa tac ccc aac tgc ttg gag tgc acc tac atc atc ttt gca Pro Glu Lys Tyr Pro Asn Cys Leu Glu Cys Thr Tyr Ile Ile Phe Ala 165 170 175	884
cca aag atg tct gag ata atc ctg gag ttt gaa agt ttt gac ctg gag Pro Lys Met Ser Glu Ile Ile Leu Glu Phe Glu Ser Phe Asp Leu Glu 180 185 190 195	932
caa gac tcg aat cct ccc gga gga atg ttc tgt cgc tat gac cgg ctg Gln Asp Ser Asn Pro Pro Gly Gly Met Phe Cys Arg Tyr Asp Arg Leu 200 205 210	980
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Leu	Asn	Tyr 310	Pro	Glu	Asn	Gly	Trp 315	Thr	Pro	Gly	Glu	Asp	Ser	Tyr	Lys	
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Glu	Trp	Ile	Gln	Val	Asp	Leu 330	Gly	Leu	Leu	Arg	Phe 335	Val	Thr	Ala	Val	
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Gln	Ala	Asp	Arg 455	Asn	Trp	Met	Pro	Glu	Asn 460	Ile	Arg	Leu	Val	Thr	Ser	
cgt	acc	ggc	tgg	gca	ctg	cca	ccc	tca	ccc	cac	cca	tac	acc	aat	gaa	1796
Arg	Thr	Gly 470	Trp	Ala	Leu	Pro	Pro 475	Ser	Pro	His	Pro	Tyr	Thr	Asn	Glu	
tgg	ctc	caa	gtg	gac	ctg	gga	gat	gag	aag	ata	gta	aga	ggc	gtc	atc	1844
Trp	Leu	Gln	Val	Asp	Leu 490	Gly	Asp	Glu	Lys	Ile	Val 495	Arg	Gly	Val	Ile	
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	615	620	625	
gcc aca gag aag cca acc att ata gac agc acc atc caa tca gag ttc Ala Thr Glu Lys Pro Thr Ile Ile Asp Ser Thr Ile Gln Ser Glu Phe				2276
	630	635	640	
ccg aca tac ggt ttt aac tgc gag ttt ggc tgg ggc tct cac aag aca Pro Thr Tyr Gly Phe Asn Cys Glu Phe Gly Trp Gly Ser His Lys Thr				2324
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	660	665	670	675
ctg acc agc aag aca ggg ccg att cag gac cat aca gga gat ggc aac Leu Thr Ser Lys Thr Gly Pro Ile Gln Asp His Thr Gly Asp Gly Asn				2420
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	695	700	705	
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	725	730	735	
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	740	745	750	755

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Gln Arg Ile Ile Ile Asn Phe Asn Pro His Phe Asp Leu Glu Asp Arg  
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Val Ser Ser Gly Pro Phe Leu Phe Ile Lys Phe Val Ser Asp Tyr Glu  
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Thr His Gly Ala Gly Phe Ser Ile Arg Tyr Glu Ile Phe Lys Arg Gly  
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Pro Glu Cys Ser Gln Asn Tyr Thr Ala Pro Thr Gly Val Ile Lys Ser  
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Ile Phe Ala Pro Lys Met Ser Glu Ile Ile Leu Glu Phe Glu Ser Phe  
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 Asp Arg Leu Glu Ile Trp Asp Gly Phe Pro Glu Val Gly Pro His Ile  
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 Gly Arg Tyr Cys Gly Gln Lys Thr Pro Gly Arg Ile Arg Ser Ser Ser  
 225 230 235 240  
 Gly Val Leu Ser Met Val Phe Tyr Thr Asp Ser Ala Ile Ala Lys Glu  
 245 250 255  
 Gly Phe Ser Ala Asn Tyr Ser Val Leu Gln Ser Ser Ile Ser Glu Asp  
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 Phe Lys Cys Met Glu Ala Leu Gly Met Glu Ser Gly Glu Ile His Ser  
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 Arg Ser Arg Leu Asn Tyr Pro Glu Asn Gly Trp Thr Pro Gly Glu Asp  
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 355 360 365  
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 Thr Asn Pro Thr Asp Val Val Leu Gly Val Phe Ser Lys Pro Leu Ile  
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 Met Arg Phe Glu Val Tyr Gly Cys Lys Ile Thr Asp Tyr Pro Cys Ser  
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Gly Met Leu Gly Met Val Ser Gly Leu Ile Ser Asp Ser Gln Ile Thr  
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Ala Ser Asn Gln Ala Asp Arg Asn Trp Met Pro Glu Asn Ile Arg Leu  
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Val Thr Ser Arg Thr Gly Trp Ala Leu Pro Pro Ser Pro His Pro Tyr  
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Thr Asn Glu Trp Leu Gln Val Asp Leu Gly Asp Glu Lys Ile Val Arg  
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Gly Val Ile Ile Gln Gly Gly Lys His Arg Glu Asn Lys Val Phe Met  
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Thr Thr Pro Asn Gly Asn Pro Val His Glu Cys Asp Asp Asp Gln Ala  
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Asn Cys His Ser Gly Thr Gly Asp Asp Phe Gln Leu Thr Gly Gly Thr  
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Thr Val Leu Ala Thr Glu Lys Pro Thr Ile Ile Asp Ser Thr Ile Gln  
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Ser Glu Phe Pro Thr Tyr Gly Phe Asn Cys Glu Phe Gly Trp Gly Ser  
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His Lys Thr Phe Cys His Trp Glu His Asp Ser His Ala Gln Leu Arg  
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Trp Ser Val Leu Thr Ser Lys Thr Gly Pro Ile Gln Asp His Thr Gly  
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Asp Gly Asn Phe Ile Tyr Ser Gln Ala Asp Glu Asn Gln Lys Gly Lys  
690 695 700

Val Ala Arg Leu Val Ser Pro Val Val Tyr Ser Gln Ser Ser Ala His  
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Cys Met Thr Phe Trp Tyr His Met Ser Gly Ser His Val Gly Thr Leu  
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Trp Met Val Val Gly His Gln Gly Asp His Trp Lys Glu Gly Arg Val  
755 760 765

Leu Leu His Lys Ser Leu Lys Leu Tyr Gln Val Ile Phe Glu Gly Glu  
770 775 780

Ile Gly Lys Gly Asn Leu Gly Gly Ile Ala Val Asp Asp Ile Ser Ile  
785 790 795 800

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805 810 815

Lys Lys Asn Thr Glu Ile Lys Ile Asp Glu Thr Gly Ser Thr Pro Gly  
820 825 830

Tyr Glu Gly Glu Gly Glu Gly Asp Lys Asn Ile Ser Arg Lys Pro Gly  
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Asn Val Leu Lys Thr Leu Asp Pro Ile Leu Ile Thr Ile Ile Ala Met  
850 855 860

Ser Ala Leu Gly Val Leu Leu Gly Ala Val Cys Gly Val Val Leu Tyr  
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Cys Ala Cys Trp His Asn Gly Met Ser Glu Arg Asn Leu Ser Ala Leu  
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&lt;222&gt; (567)..(3296)

&lt;400&gt; 7

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Phe Leu Ala Leu Tyr Phe Ser Gly His Glu Val Arg Ser Gln Gln Asp
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Ile Val Tyr Ala Pro Glu Pro Asn Gln Lys Ile Val Leu Asn Phe Asn
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Pro His Phe Glu Ile Glu Lys His Asp Cys Lys Tyr Asp Phe Ile Glu
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Pro His Asn Leu Asp Cys Thr Phe Thr Ile Leu Ala Lys Pro Arg Met	
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Gln Val Gly Glu Gly Asp Cys Lys Tyr Asp Trp Leu Asp Ile Trp Asp	
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Gly Ile Pro His Val Gly Pro Leu Ile Gly Lys Tyr Cys Gly Thr Lys	
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Thr Pro Ser Lys Leu Arg Ser Ser Thr Gly Ile Leu Ser Leu Thr Phe	
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His Thr Asp Met Ala Val Ala Lys Asp Gly Phe Ser Ala Arg Tyr Tyr	
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Leu Ile His Gln Glu Pro Pro Glu Asn Phe Gln Cys Asn Val Pro Leu	
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gga atg gag tct ggc cgg att gct aat gaa cag atc agt gcc tcc tcc	1457
Gly Met Glu Ser Gly Arg Ile Ala Asn Glu Gln Ile Ser Ala Ser Ser	
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Thr Phe Ser Asp Gly Arg Trp Thr Pro Gln Gln Ser Arg Leu His Gly	
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Asp Asp Asn Gly Trp Thr Pro Asn Leu Asp Ser Asn Lys Glu Tyr Leu	
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Gln Val Asp Leu Arg Phe Leu Thr Met Leu Thr Ala Ile Ala Thr Gln	
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Gly Ala Ile Ser Arg Glu Thr Gln Lys Gly Tyr Tyr Val Lys Ser Tyr	
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Lys Leu Glu Val Ser Thr Asn Gly Glu Asp Trp Met Val Tyr Arg His	
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Gly Lys Asn His Lys Ile Phe Gln Ala Asn Asn Asp Ala Thr Glu Val	
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Val Leu Asn Lys Leu His Met Pro Leu Leu Thr Arg Phe Ile Arg Ile	
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Trp Phe Pro Arg Asn Pro Gln Ala Gln Pro Gly Glu Glu Trp Leu Gln	
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Val Asp Leu Gly Thr Pro Lys Thr Val Lys Gly Val Ile Ile Gln Gly	
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Glu Thr Leu Gly Pro Thr Val Lys Ser Glu Glu Thr Thr Thr Pro Tyr	
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Asp Asp Lys Asn Phe Leu Lys Leu Gln Ser Asp Gly Arg Arg Glu Gly	
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Glu Tyr Glu Gly Asp Trp Ser Asn Ser Ser Ser Ser Thr Ser Gly Ala	
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&lt;212&gt; PRT

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Tyr Pro Ser His Gln Asn Cys Glu Trp Ile Val Tyr Ala Pro Glu Pro  
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Asn Gln Lys Ile Val Leu Asn Phe Asn Pro His Phe Glu Ile Glu Lys  
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His Asp Cys Lys Tyr Asp Phe Ile Glu Ile Arg Asp Gly Asp Ser Glu  
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Ser Ala Asp Leu Leu Gly Lys His Cys Gly Asn Ile Ala Pro Pro Thr  
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Ile Ile Ser Ser Gly Ser Val Leu Tyr Ile Lys Phe Thr Ser Asp Tyr  
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Glu Ser Pro Gly Phe Pro Glu Lys Tyr Pro His Asn Leu Asp Cys Thr  
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Phe Thr Ile Leu Ala Lys Pro Arg Met Glu Ile Ile Leu Gln Phe Leu  
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Thr Phe Asp Leu Glu His Asp Pro Leu Gln Val Gly Glu Gly Asp Cys  
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Lys Tyr Asp Trp Leu Asp Ile Trp Asp Gly Ile Pro His Val Gly Pro

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Thr Pro Gln Gln Ser Arg Leu His Gly Asp Asp Asn Gly Trp Thr Pro 305 310 315 320		
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Gln Thr Lys Leu Phe Glu Gly Asn Met His Tyr Asp Thr Pro Asp Ile  
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Arg Arg Phe Asp Pro Val Pro Ala Gln Tyr Val Arg Val Tyr Pro Glu  
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Asp Trp Thr Asp Ser Lys Pro Thr Val Glu Thr Leu Gly Pro Thr Val  
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Glu Cys Gly Glu Asn Cys Ser Phe Glu Asp Asp Lys Asp Leu Gln Leu  
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Pro Ser Gly Phe Asn Cys Asn Phe Asp Phe Pro Glu Glu Thr Cys Gly  
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Trp Val Tyr Asp His Ala Lys Trp Leu Arg Ser Thr Trp Ile Ser Ser  
 660 665 670

Ala Asn Pro Asn Asp Arg Thr Phe Pro Asp Asp Lys Asn Phe Leu Lys  
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Leu Gln Ser Asp Gly Arg Arg Glu Gly Gln Tyr Gly Arg Leu Ile Ser  
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Pro Pro Val His Leu Pro Arg Ser Pro Val Cys Met Glu Phe Gln Tyr  
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Gln Ala Met Gly Gly His Gly Val Ala Leu Gln Val Val Arg Glu Ala  
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Glu Trp Lys His Gly Arg Ile Ile Leu Pro Ser Tyr Asp Met Glu Tyr  
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Gln Ile Val Phe Glu Gly Val Ile Gly Lys Gly Arg Ser Gly Glu Ile  
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Ser Gly Asp Asp Ile Arg Ile Ser Thr Asp Val Pro Leu Glu Asn Cys  
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Met Glu Pro Ile Ser Ala Phe Ala Asp Glu Tyr Glu Gly Asp Trp Ser  
 805 810 815

Asn Ser Ser Ser Ser Thr Ser Gly Ala Gly Asp Pro Ser Ser Gly Lys  
 820 825 830

Glu Lys Ser Trp Leu Tyr Thr Leu Asp Pro Ile Leu Ile Thr Ile Ile  
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Ala Met Ser Ser Leu Gly Val Leu Leu Gly Ala Thr Cys Ala Gly Leu  
 850 855 860

Leu Leu Tyr Cys Thr Cys Ser Tyr Ser Gly Leu Ser Ser Arg Ser Cys  
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<221> CDS

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Val Pro Arg Leu Lys Leu Ser Tyr Lys Glu Met Leu Glu Ser Asn Asn	
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Val Ile Thr Phe Asn Gly Leu Ala Asn Ser Ser Ser Tyr His Thr Phe	
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Leu Leu Asp Glu Glu Arg Ser Arg Leu Tyr Val Gly Ala Lys Asp His	
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ata ttt tca ttc gac ctg gtt aat atc aag gat ttt caa aag att gtg	291
Ile Phe Ser Phe Asp Leu Val Asn Ile Lys Asp Phe Gln Lys Ile Val	
80 85 90	
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Trp Pro Val Ser Tyr Thr Arg Arg Asp Glu Cys Lys Trp Ala Gly Lys	
95 100 105	
gac atc ctg aaa gaa tgt gct aat ttc atc aag gta ctt aag gca tat	387
Asp Ile Leu Lys Glu Cys Ala Asn Phe Ile Lys Val Leu Lys Ala Tyr	
110 115 120	
aat cag act cac ttg tac gcc tgt gga acg ggg gct ttt cat cca att	435
Asn Gln Thr His Leu Tyr Ala Cys Gly Thr Gly Ala Phe His Pro Ile	
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Cys Thr Tyr Ile Glu Ile Gly His His Pro Glu Asp Asn Ile Phe Lys	
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Leu Glu Asn Ser His Phe Glu Asn Gly Arg Gly Lys Ser Pro Tyr Asp	
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Leu Gly His His His Pro Ile Arg Thr Glu Gln His Asp Ser Arg Trp	
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Leu	Glu	Glu	Met	Thr	Val	Phe	Arg	Glu	Pro	Thr	Ala	Ile	Ser	Ala	Met	
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Glu	Leu	Ser	Thr	Lys	Gln	Gln	Gln	Leu	Tyr	Ile	Gly	Ser	Thr	Ala	Gly	
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Ala	Glu	Cys	Cys	Leu	Ala	Arg	Asp	Pro	Tyr	Cys	Ala	Trp	Asp	Gly	Ser	
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Ala	Cys	Ser	Arg	Tyr	Phe	Pro	Thr	Ala	Lys	Arg	Arg	Thr	Arg	Arg	Gln	
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Val	Trp	Tyr	Arg	Asp	Phe	Met	Gln	Leu	Ile	Asn	His	Pro	Asn	Leu	Asn	



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Arg Arg Gln Arg Pro Gly His Thr Pro Gly Asn Ser Asn Lys Trp Lys				
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His Leu Gln Glu Asn Lys Lys Gly Arg Asn Arg Arg Thr His Glu Phe				
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Glu Arg Ala Pro Arg Ser Val				
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Lys Phe Ile Ser Ala His Leu Ile Ser Glu Ser Asp Asn Pro Glu Asp  
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 Ile Gln Thr Leu Leu Lys Val Thr Leu Glu Val Ile Asp Thr Glu His  
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 Leu Glu Glu Leu Leu His Lys Asp Asp Asp Gly Asp Gly Ser Lys Thr  
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 Lys Glu Met Ser Asn Ser Met Thr Pro Ser Gln Lys Val Trp Tyr Arg  
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 Phe Cys Glu Gln Val Trp Lys Arg Asp Arg Lys Gln Arg Arg Gln Arg  
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Ala Val Gly Leu Gly Ser Ala Ala Pro Ser Pro Pro Arg Leu Arg Leu	20 25 30
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Ser Phe Gln Glu Leu Gln Ala Trp His Gly Leu Gln Thr Phe Ser Leu	35 40 45
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Glu Arg Thr Cys Cys Tyr Gln Ala Leu Leu Val Asp Glu Glu Arg Gly	50 55 60 65
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Asn Ile Ser Lys Arg Ala Lys Lys Leu Ala Trp Pro Ala Pro Val Glu	85 90 95
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Trp Arg Glu Glu Cys Asn Trp Ala Gly Lys Asp Ile Gly Thr Glu Cys	100 105 110
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Met Gly Arg Asp Phe Thr Ile Phe Arg Ser Leu Gly Gln Arg Pro Ser	195 200 205
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Ile Tyr Phe Phe Phe Arg Glu Thr Ala Val Glu Ala Ala Pro Ala Leu	
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Ile Gly Thr Asp Val Gly Thr Val Leu Lys Val Ile Ser Val Pro Lys	
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cgg	gac	ttt	ctg	cag	ctg	gtg	gag	ccg	ggc	gga	ggt	ggc	agc	gcg	aac	2350
Arg	Asp	Phe	Leu	Gln	Leu	Val	Glu	Pro	Gly	Gly	Gly	Gly	Ser	Ala	Asn	
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Arg Ala Glu Arg Gly Pro Arg Ser Ala Thr His Trp				
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&lt;210&gt; 12

&lt;211&gt; 749

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 12

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Phe Gly Thr Phe Ser Ser Thr Lys Asp Phe Pro Asp Asp Val Ile Gln  
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Gly Arg Pro Leu Phe Leu Gln Val Gly Ala Asn Tyr Thr Phe Thr Gln  
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Ile Ala Ala Asp Arg Val Ala Ala Ala Asp Gly His Tyr Asp Val Leu  
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Phe Ile Gly Thr Asp Val Gly Thr Val Leu Lys Val Ile Ser Val Pro  
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Lys Gly Ser Arg Pro Ser Ala Glu Gly Leu Leu Leu Glu Glu Leu His  
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Leu His Arg Cys Ala Ala His Gly Arg Val Cys Thr Glu Cys Cys Leu  
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Gln Pro Ser Ala Lys Arg Arg Phe Arg Arg Gln Asp Val Arg Asn Gly  
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Asp Pro Ser Thr Leu Cys Ser Gly Asp Ser Ser Arg Pro Ala Leu Leu  
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Glu His Lys Val Phe Gly Val Glu Gly Ser Ser Ala Phe Leu Glu Cys  
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Glu Pro Arg Ser Leu Gln Ala Arg Val Glu Trp Thr Phe Gln Arg Ala  
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Gly Val Thr Ala His Thr Gln Val Leu Ala Glu Glu Arg Thr Glu Arg  
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Thr Ala Arg Gly Leu Leu Leu Arg Arg Leu Arg Arg Arg Asp Ser Gly  
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Arg Ala Glu Glu Ala Ala Pro Ala Ala Pro Pro Gly Pro Lys Leu Trp  
675 680 685

Tyr Arg Asp Phe Leu Gln Leu Val Glu Pro Gly Gly Gly Gly Ser Ala  
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Pro Arg Ala Glu Arg Gly Pro Arg Ser Ala Thr His Trp  
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<222> (563)..(2818)

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Gly Val Phe Ile Cys Ser Ile Cys Val Lys Gly Ser Ser Gln Pro Gln	
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Glu Tyr Phe Ser Leu Ser His His Pro Leu Asp Tyr Arg Ile Leu Leu	
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Ser	Glu	Pro	Met	Phe	Val	Asp	Ala	His	Val	Ile	Pro	Asp	Gly	Thr	Asp	
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&lt;210&gt; 14

&lt;211&gt; 751

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 14

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His His Pro Leu Asp Tyr Arg Ile Leu Leu Met Asp Glu Asp Gln Asp
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 Asp Ala His Val Ile Pro Asp Gly Thr Asp Pro Asn Asp Ala Lys Val  
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**55/110**

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Ser Gln Gly Leu Leu Ile Arg Ser Val Gln Gly Ser Asp Gln Gly Leu  
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Tyr His Cys Ile Ala Thr Glu Asn Ser Phe Lys Gln Thr Ile Ala Lys  
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Ile Asn Phe Lys Val Leu Asp Ser Glu Met Val Ala Val Val Thr Asp  
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 690 695 700

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Trp Ser Arg Asp Ala Ala Ile Phe Arg Ser Met Gly Arg Leu Ala His	
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Ile Arg Thr Glu His Asp Asp Glu Arg Leu Leu Lys Glu Pro Lys Phe	
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Val Gly Ser Tyr Met Ile Pro Asp Asn Glu Asp Arg Asp Asp Asn Lys	
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Val Tyr Phe Phe Phe Thr Glu Lys Ala Leu Glu Ala Glu Asn Asn Ala	
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His Ala Ile Tyr Thr Arg Val Gly Arg Leu Cys Val Asn Asp Val Gly	
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Gly Gln Arg Ile Leu Val Asn Lys Trp Ser Thr Phe Leu Lys Ala Arg	
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Pro Tyr Ala His Lys Glu Gly Pro Glu Tyr His Trp Ser Val Tyr Glu	
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Thr	Asp	Asp	Arg	Val	Val	Lys	Met	Asp	Leu	Gly	Leu	Leu	Phe	Leu	Arg		
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His Arg Met Pro Cys Pro Ala Gln Ser Ser Ile Ser Gln Gly Ala Lys	695	700	705	
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Pro Trp Tyr Lys Glu Phe Leu Gln Leu Ile Gly Tyr Ser Asn Phe Gln	710	715	720	
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Phe His Ser Pro Phe Gly Phe Leu Asp Leu His Thr Met Leu Leu Asp  
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Glu Tyr Gln Glu Arg Leu Phe Val Gly Gly Arg Asp Leu Val Tyr Ser  
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Leu Ser Leu Glu Arg Ile Ser Asp Gly Tyr Lys Glu Ile His Trp Pro  
85 90 95

Ser Thr Ala Leu Lys Met Glu Glu Cys Ile Met Lys Gly Lys Asp Ala  
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Gly Glu Cys Ala Asn Tyr Val Arg Val Leu His His Tyr Asn Arg Thr  
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Val Tyr Glu Gly Lys Val Pro Tyr Pro Arg Pro Gly Ser Cys Ala Ser  
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Lys Val Asn Gly Gly Arg Tyr Gly Thr Thr Lys Asp Tyr Pro Asp Asp  
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Pro Ala His Lys Lys Pro Ile Leu Val Lys Thr Asp Gly Lys Tyr Asn  
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Thr Ile Tyr Asn Gln Glu Met Glu Ser Met Glu Glu Val Ile Leu Glu  
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Glu Leu Gln Ile Phe Lys Asp Pro Val Pro Ile Ile Ser Met Glu Ile  
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Gln Asp Val Arg His Gly Asn Ala Ala Gln Gln Cys Phe Gly Gln Gln  
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Phe Val Gly Asp Ala Leu Asp Lys Thr Glu Glu His Leu Ala Tyr Gly  
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Ile Glu Asn Asn Ser Thr Leu Leu Glu Cys Thr Pro Arg Ser Leu Gln  
 595 600 605

Ala Lys Val Ile Trp Phe Val Gln Lys Gly Arg Glu Thr Arg Lys Glu

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60					65				70					75		
tac	gtg	ctg	tcc	ctg	gac	ctg	cac	gac	atc	aac	cgc	gag	ccc	ctc	att	351
Tyr	Val	Leu	Ser	Leu	Asp	Leu	His	Asp	Ile	Asn	Arg	Glu	Pro	Leu	Ile	
				80					85					90		
ata	cac	tgg	gca	gcc	tcc	cca	cag	cgc	atc	gag	gaa	tgc	gtg	ctc	tca	399
Ile	His	Trp	Ala	Ala	Ser	Pro	Gln	Arg	Ile	Glu	Glu	Cys	Val	Leu	Ser	
			95				100					105				
ggc	aag	gat	gtc	aac	ggc	gag	tgt	ggg	aac	ttc	gtc	agg	ctc	atc	cag	447
Gly	Lys	Asp	Val	Asn	Gly	Glu	Cys	Gly	Asn	Phe	Val	Arg	Leu	Ile	Gln	
		110					115					120				
ccc	tgg	aac	cga	aca	cac	ctg	tat	gtg	tgc	ggg	aca	ggt	gcc	tac	aac	495
Pro	Trp	Asn	Arg	Thr	His	Leu	Tyr	Val	Cys	Gly	Thr	Gly	Ala	Tyr	Asn	
			125				130				135					
ccc	atg	tgc	acc	tat	gtg	aac	cgc	gga	cgc	cgc	gcc	cag	gcc	aca	cca	543
Pro	Met	Cys	Thr	Tyr	Val	Asn	Arg	Gly	Arg	Arg	Ala	Gln	Ala	Thr	Pro	
140					145				150						155	
tgg	acc	cag	act	cag	gcg	gtc	aga	ggc	cgc	ggc	agc	aga	gcc	acg	gat	591
Trp	Thr	Gln	Thr	Gln	Ala	Val	Arg	Gly	Arg	Gly	Ser	Arg	Ala	Thr	Asp	
				160					165					170		
ggt	gcc	ctc	cgc	cgg	atg	ccc	aca	gcc	cca	cgc	cag	gat	tac	atc	ttc	639
Gly	Ala	Leu	Arg	Pro	Met	Pro	Thr	Ala	Pro	Arg	Gln	Asp	Tyr	Ile	Phe	
			175					180					185			
tac	ctg	gag	cct	gag	cga	ctc	gag	tca	ggg	aag	ggc	aag	tgt	ccg	tac	687
Tyr	Leu	Glu	Pro	Glu	Arg	Leu	Glu	Ser	Gly	Lys	Gly	Lys	Cys	Pro	Tyr	
			190				195					200				
gat	ccc	aag	ctg	gac	aca	gca	tcg	gcc	ctc	atc	aat	gag	gag	ctc	tat	735
Asp	Pro	Lys	Leu	Asp	Thr	Ala	Ser	Ala	Leu	Ile	Asn	Glu	Glu	Leu	Tyr	
			205			210					215					
gct	ggt	gtg	tac	atc	gat	ttt	atg	ggc	act	gat	gca	gcc	atc	ttc	cgc	783
Ala	Gly	Val	Tyr	Ile	Asp	Phe	Met	Gly	Thr	Asp	Ala	Ala	Ile	Phe	Arg	
220					225					230					235	
aca	ctt	gga	aag	cag	aca	gcc	atg	cgc	acg	gat	cag	tac	aac	tcc	cgg	831
Thr	Leu	Gly	Lys	Gln	Thr	Ala	Met	Arg	Thr	Asp	Gln	Tyr	Asn	Ser	Arg	
				240					245					250		

tgg ctg aac gac ccg tcg ttc atc cat gct gag ctc att cct gac agt	879
Trp Leu Asn Asp Pro Ser Phe Ile His Ala Glu Leu Ile Pro Asp Ser	
255 260 265	
gcg gag cgc aat gat gat aag ctt tac ttc ttc ttc cgt gag cgg tcg	927
Ala Glu Arg Asn Asp Asp Lys Leu Tyr Phe Phe Phe Arg Glu Arg Ser	
270 275 280	
gca gag gcg ccg cag agc ccc gcg gtg tac gcc cgc atc ggg cgc att	975
Ala Glu Ala Pro Gln Ser Pro Ala Val Tyr Ala Arg Ile Gly Arg Ile	
285 290 295	
tgc ctg aac gat gac ggt ggt cac tgt tgc ctg gtc aac aag tgg agc	1023
Cys Leu Asn Asp Asp Gly Gly His Cys Cys Leu Val Asn Lys Trp Ser	
300 305 310 315	
aca ttc ctg aag gcg cgg ctc gtc tgc tct gtc ccg ggc gag gat ggc	1071
Thr Phe Leu Lys Ala Arg Leu Val Cys Ser Val Pro Gly Glu Asp Gly	
320 325 330	
att gag act cac ttt gat gag ctc cag gac gtg ttt gtc cag cag acc	1119
Ile Glu Thr His Phe Asp Glu Leu Gln Asp Val Phe Val Gln Gln Thr	
335 340 345	
cag gac gtg agg aac cct gtc att tac gct gtc ttt acc tcc tct ggc	1167
Gln Asp Val Arg Asn Pro Val Ile Tyr Ala Val Phe Thr Ser Ser Gly	
350 355 360	
tcc gtg ttc cga ggc tct gcc gtg tgt gtc tac tcc atg gct gat att	1215
Ser Val Phe Arg Gly Ser Ala Val Cys Val Tyr Ser Met Ala Asp Ile	
365 370 375	
cgc atg gtc ttc aac ggg ccc ttt gcc cac aaa gag ggg ccc aac tac	1263
Arg Met Val Phe Asn Gly Pro Phe Ala His Lys Glu Gly Pro Asn Tyr	
380 385 390 395	
cag tgg atg ccc ttc tca ggg aag atg ccc tac cca cgg ccg ggc acg	1311
Gln Trp Met Pro Phe Ser Gly Lys Met Pro Tyr Pro Arg Pro Gly Thr	
400 405 410	
tgc cct ggt gga acc ttc acg cca tct atg aag tcc acc aag gat tat	1359
Cys Pro Gly Gly Thr Phe Thr Pro Ser Met Lys Ser Thr Lys Asp Tyr	
415 420 425	
cct gat gag gtg atc aac ttc atg cgc agc cac cca ctc atg tac cag	1407
Pro Asp Glu Val Ile Asn Phe Met Arg Ser His Pro Leu Met Tyr Gln	
430 435 440	
gcc gtg tac cct ctg cag cgg cgg ccc ctg gta gtc cgc aca ggt gct	1455
Ala Val Tyr Pro Leu Gln Arg Arg Pro Leu Val Val Arg Thr Gly Ala	
445 450 455	
ccc tac cgc ctt acc act att gcc gtg gac cag gtg gat gca ggc gac	1503
Pro Tyr Arg Leu Thr Thr Ile Ala Val Asp Gln Val Asp Ala Gly Asp	
460 465 470 475	
ggg cgc tat gag gtg ctt ttc ctg ggc aca gac cgc ggg aca gtg cag	1551
Gly Arg Tyr Glu Val Leu Phe Leu Gly Thr Asp Arg Gly Thr Val Gln	
480 485 490	
aag gtc att gtg ctg ccc aag gat gac cag gag atg gag gag ctc atg	1599

Lys	Val	Ile	Val	Leu	Pro	Lys	Asp	Asp	Gln	Glu	Met	Glu	Glu	Leu	Met	
			495					500					505			
ctg	gag	gag	gtg	gag	gtc	ttc	aag	gat	cca	gca	ccc	gtc	aag	acc	atg	1647
Leu	Glu	Glu	Val	Glu	Val	Phe	Lys	Asp	Pro	Ala	Pro	Val	Lys	Thr	Met	
			510				515					520				
acc	atc	tct	tct	aag	agg	caa	caa	ctc	tac	gtg	gcg	tca	gcc	gtg	ggt	1695
Thr	Ile	Ser	Ser	Lys	Arg	Gln	Gln	Leu	Tyr	Val	Ala	Ser	Ala	Val	Gly	
			525				530				535					
gtc	aca	cac	ctg	agc	ctg	cac	cgc	tgc	cag	gcg	tat	ggg	gct	gcc	tgt	1743
Val	Thr	His	Leu	Ser	Leu	His	Arg	Cys	Gln	Ala	Tyr	Gly	Ala	Ala	Cys	
			540				545				550				555	
gct	gac	tgc	tgc	ctt	gcc	cgg	gac	cct	tac	tgt	gcc	tgg	gat	ggc	cag	1791
Ala	Asp	Cys	Cys	Leu	Ala	Arg	Asp	Pro	Tyr	Cys	Ala	Trp	Asp	Gly	Gln	
				560					565						570	
gcc	tgc	tcc	cgc	tat	aca	gca	tcc	tcc	aag	agg	cgg	agc	cgc	cgg	cag	1839
Ala	Cys	Ser	Arg	Tyr	Thr	Ala	Ser	Ser	Lys	Arg	Arg	Ser	Arg	Arg	Gln	
			575					580					585			
gac	gtc	cgg	cac	gga	aac	ccc	atc	agg	cag	tgc	cgt	ggg	ttc	aac	tcc	1887
Asp	Val	Arg	His	Gly	Asn	Pro	Ile	Arg	Gln	Cys	Arg	Gly	Phe	Asn	Ser	
			590				595					600				
aat	gcc	aac	aag	aat	gcc	gtg	gag	tct	gtg	cag	tat	ggc	gtg	gcc	ggc	1935
Asn	Ala	Asn	Lys	Asn	Ala	Val	Glu	Ser	Val	Gln	Tyr	Gly	Val	Ala	Gly	
			605				610				615					
agc	gca	gcc	ttc	ctt	gag	tgc	cag	ccc	cgc	tcg	ccc	caa	gcc	act	gtt	1983
Ser	Ala	Ala	Phe	Leu	Glu	Cys	Gln	Pro	Arg	Ser	Pro	Gln	Ala	Thr	Val	
			620				625				630				635	
aag	tgg	ctg	ttc	cag	cga	gat	cct	ggt	gac	cgg	cgc	cga	gag	att	cgt	2031
Lys	Trp	Leu	Phe	Gln	Arg	Asp	Pro	Gly	Asp	Arg	Arg	Arg	Glu	Ile	Arg	
				640					645						650	
gca	gag	gac	cgc	ttc	ctg	cgc	aca	gag	cag	ggc	ttg	ttg	ctc	cgt	gca	2079
Ala	Glu	Asp	Arg	Phe	Leu	Arg	Thr	Glu	Gln	Gly	Leu	Leu	Leu	Arg	Ala	
			655						660						665	
ctg	cag	ctc	agc	gat	cgt	ggc	ctc	tac	tcc	tgc	aca	gcc	act	gag	aac	2127
Leu	Gln	Leu	Ser	Asp	Arg	Gly	Leu	Tyr	Ser	Cys	Thr	Ala	Thr	Glu	Asn	
			670				675					680				
aac	ttt	aag	cac	gtc	gtc	aca	cga	gtg	cag	ctg	cat	gta	ctg	ggc	cgg	2175
Asn	Phe	Lys	His	Val	Val	Thr	Arg	Val	Gln	Leu	His	Val	Leu	Gly	Arg	
			685				690				695					
gac	gcc	gtc	cat	gct	gcc	ctc	ttc	cca	cca	ctg	tcc	atg	agc	gcc	ccg	2223
Asp	Ala	Val	His	Ala	Ala	Leu	Phe	Pro	Pro	Leu	Ser	Met	Ser	Ala	Pro	
						705					710				715	
cca	ccc	cca	ggc	gca	ggc	ccc	cca	acg	cct	cct	tac	cag	gag	tta	gcc	2271
Pro	Pro	Pro	Gly	Ala	Gly	Pro	Pro	Thr	Pro	Pro	Tyr	Gln	Glu	Leu	Ala	
				720					725						730	
cag	ctg	ctg	gcc	cag	cca	gaa	gtg	ggc	ctc	atc	cac	cag	tac	tgc	cag	2319
Gln	Leu	Leu	Ala	Gln	Pro	Glu	Val	Gly	Leu	Ile	His	Gln	Tyr	Cys	Gln	

735	740	745	
ggt tac tgg cgc cat gtg ccc ccc agc ccc agg gag gct cca ggg gca			2367
Gly Tyr Trp Arg His Val Pro Pro Ser Pro Arg Glu Ala Pro Gly Ala			
750	755	760	
ccc cgg tct cct gag ccc cag gac cag aaa aag ccc cgg aac cgc cgg			2415
Pro Arg Ser Pro Glu Pro Gln Asp Gln Lys Lys Pro Arg Asn Arg Arg			
765	770	775	
cac cac cct ccg gac aca tga ggccagctgc ctgtgcctgc catgggccag			2466
His His Pro Pro Asp Thr			
780	785		
gctaggcctt ggtccctttt aatataaaag atatatatat atatatatat atatattaaa			2526
atatcgggggt ggggggtgat tggaaggagg ggaggtggcc ttcccaatgc gcgttattcg			2586
gggttattga agaataatat tgcaagtgac agccagaagt agactttctg tcctcacacc			2646
gaagaacccg agtgagcagg agggagggag agacgcgaag agaccttttt tcctttttgg			2706
agaccttgtc cgc			2719
<210> 18			
<211> 785			
<212> PRT			
<213> Homo sapiens			
<400> 18			
Met Leu Val Ala Gly Leu Leu Leu Trp Ala Ser Leu Leu Thr Gly Ala			
1	5	10	15
Trp Pro Ser Phe Pro Thr Gln Asp His Leu Pro Ala Thr Pro Arg Val			
	20	25	30
Arg Leu Ser Phe Lys Glu Leu Lys Ala Thr Gly Thr Ala His Phe Phe			
	35	40	45
Asn Phe Leu Leu Asn Thr Thr Asp Tyr Arg Ile Leu Leu Lys Asp Glu			
	50	55	60
Asp His Asp Arg Met Tyr Val Gly Ser Lys Asp Tyr Val Leu Ser Leu			
65	70	75	80
Asp Leu His Asp Ile Asn Arg Glu Pro Leu Ile Ile His Trp Ala Ala			
	85	90	95
Ser Pro Gln Arg Ile Glu Glu Cys Val Leu Ser Gly Lys Asp Val Asn			
	100	105	110



Gly Glu Cys Gly Asn Phe Val Arg Leu Ile Gln Pro Trp Asn Arg Thr  
 115 120 125  
 His Leu Tyr Val Cys Gly Thr Gly Ala Tyr Asn Pro Met Cys Thr Tyr  
 130 135 140  
 Val Asn Arg Gly Arg Arg Ala Gln Ala Thr Pro Trp Thr Gln Thr Gln  
 145 150 155 160  
 Ala Val Arg Gly Arg Gly Ser Arg Ala Thr Asp Gly Ala Leu Arg Pro  
 165 170 175  
 Met Pro Thr Ala Pro Arg Gln Asp Tyr Ile Phe Tyr Leu Glu Pro Glu  
 180 185 190  
 Arg Leu Glu Ser Gly Lys Gly Lys Cys Pro Tyr Asp Pro Lys Leu Asp  
 195 200 205  
 Thr Ala Ser Ala Leu Ile Asn Glu Glu Leu Tyr Ala Gly Val Tyr Ile  
 210 215 220  
 Asp Phe Met Gly Thr Asp Ala Ala Ile Phe Arg Thr Leu Gly Lys Gln  
 225 230 235 240  
 Thr Ala Met Arg Thr Asp Gln Tyr Asn Ser Arg Trp Leu Asn Asp Pro  
 245 250 255  
 Ser Phe Ile His Ala Glu Leu Ile Pro Asp Ser Ala Glu Arg Asn Asp  
 260 265 270  
 Asp Lys Leu Tyr Phe Phe Phe Arg Glu Arg Ser Ala Glu Ala Pro Gln  
 275 280 285  
 Ser Pro Ala Val Tyr Ala Arg Ile Gly Arg Ile Cys Leu Asn Asp Asp  
 290 295 300  
 Gly Gly His Cys Cys Leu Val Asn Lys Trp Ser Thr Phe Leu Lys Ala  
 305 310 315 320  
 Arg Leu Val Cys Ser Val Pro Gly Glu Asp Gly Ile Glu Thr His Phe  
 325 330 335  
 Asp Glu Leu Gln Asp Val Phe Val Gln Gln Thr Gln Asp Val Arg Asn  
 340 345 350  
 Pro Val Ile Tyr Ala Val Phe Thr Ser Ser Gly Ser Val Phe Arg Gly  
 355 360 365

Ser Ala Val Cys Val Tyr Ser Met Ala Asp Ile Arg Met Val Phe Asn  
 370 375 380

Gly Pro Phe Ala His Lys Glu Gly Pro Asn Tyr Gln Trp Met Pro Phe  
 385 390 395 400

Ser Gly Lys Met Pro Tyr Pro Arg Pro Gly Thr Cys Pro Gly Gly Thr  
 405 410 415

Phe Thr Pro Ser Met Lys Ser Thr Lys Asp Tyr Pro Asp Glu Val Ile  
 420 425 430

Asn Phe Met Arg Ser His Pro Leu Met Tyr Gln Ala Val Tyr Pro Leu  
 435 440 445

Gln Arg Arg Pro Leu Val Val Arg Thr Gly Ala Pro Tyr Arg Leu Thr  
 450 455 460

Thr Ile Ala Val Asp Gln Val Asp Ala Gly Asp Gly Arg Tyr Glu Val  
 465 470 475 480

Leu Phe Leu Gly Thr Asp Arg Gly Thr Val Gln Lys Val Ile Val Leu  
 485 490 495

Pro Lys Asp Asp Gln Glu Met Glu Glu Leu Met Leu Glu Glu Val Glu  
 500 505 510

Val Phe Lys Asp Pro Ala Pro Val Lys Thr Met Thr Ile Ser Ser Lys  
 515 520 525

Arg Gln Gln Leu Tyr Val Ala Ser Ala Val Gly Val Thr His Leu Ser  
 530 535 540

Leu His Arg Cys Gln Ala Tyr Gly Ala Ala Cys Ala Asp Cys Cys Leu  
 545 550 555 560

Ala Arg Asp Pro Tyr Cys Ala Trp Asp Gly Gln Ala Cys Ser Arg Tyr  
 565 570 575

Thr Ala Ser Ser Lys Arg Arg Ser Arg Arg Gln Asp Val Arg His Gly  
 580 585 590

Asn Pro Ile Arg Gln Cys Arg Gly Phe Asn Ser Asn Ala Asn Lys Asn  
 595 600 605

Ala Val Glu Ser Val Gln Tyr Gly Val Ala Gly Ser Ala Ala Phe Leu  
 610 615 620

Glu Cys Gln Pro Arg Ser Pro Gln Ala Thr Val Lys Trp Leu Phe Gln  
 625 630 635 640

Arg Asp Pro Gly Asp Arg Arg Arg Glu Ile Arg Ala Glu Asp Arg Phe  
 645 650 655

Leu Arg Thr Glu Gln Gly Leu Leu Leu Arg Ala Leu Gln Leu Ser Asp  
 660 665 670

Arg Gly Leu Tyr Ser Cys Thr Ala Thr Glu Asn Asn Phe Lys His Val  
 675 680 685

Val Thr Arg Val Gln Leu His Val Leu Gly Arg Asp Ala Val His Ala  
 690 695 700

Ala Leu Phe Pro Pro Leu Ser Met Ser Ala Pro Pro Pro Pro Gly Ala  
 705 710 715 720

Gly Pro Pro Thr Pro Pro Tyr Gln Glu Leu Ala Gln Leu Leu Ala Gln  
 725 730 735

Pro Glu Val Gly Leu Ile His Gln Tyr Cys Gln Gly Tyr Trp Arg His  
 740 745 750

Val Pro Pro Ser Pro Arg Glu Ala Pro Gly Ala Pro Arg Ser Pro Glu  
 755 760 765

Pro Gln Asp Gln Lys Lys Pro Arg Asn Arg Arg His His Pro Pro Asp  
 770 775 780

Thr  
 785

<210> 19

<211> 649

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (17)..(592)

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (17)..(94)

&lt;223&gt; Signal peptide

&lt;400&gt; 19

tcgggcctcc gaaacc atg aac ttt ctg ctg tct tgg gtg cat tgg agc ctt	52
Met Asn Phe Leu Leu Ser Trp Val His Trp Ser Leu	
1 5 10	
gcc ttg ctg ctc tac ctc cac cat gcc aag tgg tcc cag gct gca ccc	100
Ala Leu Leu Leu Tyr Leu His His Ala Lys Trp Ser Gln Ala Ala Pro	
15 20 25	
atg gca gaa gga gga ggg cag aat cat cac gaa gtg gtg aag ttc atg	148
Met Ala Glu Gly Gly Gly Gln Asn His His Glu Val Val Lys Phe Met	
30 35 40	
gat gtc tat cag cgc agc tac tgc cat cca atc gag acc ctg gtg gac	196
Asp Val Tyr Gln Arg Ser Tyr Cys His Pro Ile Glu Thr Leu Val Asp	
45 50 55 60	
atc ttc cag gag tac cct gat gag atc gag tac atc ttc aag cca tcc	244
Ile Phe Gln Glu Tyr Pro Asp Glu Ile Glu Tyr Ile Phe Lys Pro Ser	
65 70 75	
tgt gtg ccc ctg atg cga tgc ggg ggc tgc tgc aat gac gag ggc ctg	292
Cys Val Pro Leu Met Arg Cys Gly Gly Cys Cys Asn Asp Glu Gly Leu	
80 85 90	
gag tgt gtg ccc act gag gag tcc aac atc acc atg cag att atg cgg	340
Glu Cys Val Pro Thr Glu Glu Ser Asn Ile Thr Met Gln Ile Met Arg	
95 100 105	
atc aaa cct cac caa ggc cag cac ata gga gag atg agc ttc cta cag	388
Ile Lys Pro His Gln Gly Gln His Ile Gly Glu Met Ser Phe Leu Gln	
110 115 120	
cac aac aaa tgt gaa tgc aga cca aag aaa gat aga gca aga caa gaa	436
His Asn Lys Cys Glu Cys Arg Pro Lys Lys Asp Arg Ala Arg Gln Glu	
125 130 135 140	
aat ccc tgt ggg cct tgc tca gag cgg aga aag cat ttg ttt gta caa	484
Asn Pro Cys Gly Pro Cys Ser Glu Arg Arg Lys His Leu Phe Val Gln	
145 150 155	
gat ccg cag acg tgt aaa tgt tcc tgc aaa aac aca gac tcg cgt tgc	532
Asp Pro Gln Thr Cys Lys Cys Ser Cys Lys Asn Thr Asp Ser Arg Cys	
160 165 170	
aag gcg agg cag ctt gag tta aac gaa cgt act tgc aga tgt gac aag	580
Lys Ala Arg Gln Leu Glu Leu Asn Glu Arg Thr Cys Arg Cys Asp Lys	
175 180 185	
ccg agg cgg tga gccgggcagg aggaaggagc ctccctcagc gtttcgggaa	632
Pro Arg Arg	
190	

ccagatctct caccagg

649

&lt;210&gt; 20

&lt;211&gt; 191

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (17)..(94)

&lt;223&gt; Signal peptide

&lt;400&gt; 20

Met Asn Phe Leu Leu Ser Trp Val His Trp Ser Leu Ala Leu Leu Leu  
 1 5 10 15

Tyr Leu His His Ala Lys Trp Ser Gln Ala Ala Pro Met Ala Glu Gly  
 20 25 30

Gly Gly Gln Asn His His Glu Val Val Lys Phe Met Asp Val Tyr Gln  
 35 40 45

Arg Ser Tyr Cys His Pro Ile Glu Thr Leu Val Asp Ile Phe Gln Glu  
 50 55 60

Tyr Pro Asp Glu Ile Glu Tyr Ile Phe Lys Pro Ser Cys Val Pro Leu  
 65 70 75 80

Met Arg Cys Gly Gly Cys Cys Asn Asp Glu Gly Leu Glu Cys Val Pro  
 85 90 95

Thr Glu Glu Ser Asn Ile Thr Met Gln Ile Met Arg Ile Lys Pro His  
 100 105 110

Gln Gly Gln His Ile Gly Glu Met Ser Phe Leu Gln His Asn Lys Cys  
 115 120 125

Glu Cys Arg Pro Lys Lys Asp Arg Ala Arg Gln Glu Asn Pro Cys Gly  
 130 135 140

Pro Cys Ser Glu Arg Arg Lys His Leu Phe Val Gln Asp Pro Gln Thr  
 145 150 155 160

Cys Lys Cys Ser Cys Lys Asn Thr Asp Ser Arg Cys Lys Ala Arg Gln  
 165 170 175

Leu Glu Leu Asn Glu Arg Thr Cys Arg Cys Asp Lys Pro Arg Arg  
 180 185 190

<210> 21

<211> 755

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (5)..(628)

<400> 21

cacc atg agc cct ctg ctc cgc cgc ctg ctg ctc gcc gca ctc ctg cag 49  
 Met Ser Pro Leu Leu Arg Arg Leu Leu Leu Ala Ala Leu Leu Gln  
 1 5 10 15

ctg gcc ccc gcc cag gcc cct gtc tcc cag cct gat gcc cct ggc cac 97  
 Leu Ala Pro Ala Gln Ala Pro Val Ser Gln Pro Asp Ala Pro Gly His  
 20 25 30

cag agg aaa gtg gtg tca tgg ata gat gtg tat act cgc gct acc tgc 145  
 Gln Arg Lys Val Val Ser Trp Ile Asp Val Tyr Thr Arg Ala Thr Cys  
 35 40 45

cag ccc cgg gag gtg gtg gtg ccc ttg act gtg gag ctc atg ggc acc 193  
 Gln Pro Arg Glu Val Val Val Pro Leu Thr Val Glu Leu Met Gly Thr  
 50 55 60

gtg gcc aaa cag ctg gtg ccc agc tgc gtg act gtg cag cgc tgt ggt 241  
 Val Ala Lys Gln Leu Val Pro Ser Cys Val Thr Val Gln Arg Cys Gly  
 65 70 75

ggc tgc tgc cct gac gat ggc ctg gag tgt gtg ccc act ggg cag cac 289  
 Gly Cys Cys Pro Asp Asp Gly Leu Glu Cys Val Pro Thr Gly Gln His  
 80 85 90 95

caa gtc cgg atg cag atc ctc atg atc cgg tac ccg agc agt cag ctg 337  
 Gln Val Arg Met Gln Ile Leu Met Ile Arg Tyr Pro Ser Ser Gln Leu  
 100 105 110

ggg gag atg tcc ctg gaa gaa cac agc cag tgt gaa tgc aga cct aaa 385  
 Gly Glu Met Ser Leu Glu Glu His Ser Gln Cys Glu Cys Arg Pro Lys  
 115 120 125

aaa aag gac agt gct gtg aag cca gac agg gct gcc act ccc cac cac 433  
 Lys Lys Asp Ser Ala Val Lys Pro Asp Arg Ala Ala Thr Pro His His

130	135	140	
cgt ccc cag ccc cgt tct gtt ccg ggc tgg gac tct gcc ccc gga gca			481
Arg Pro Gln Pro Arg Ser Val Pro Gly Trp Asp Ser Ala Pro Gly Ala			
145	150	155	
ccc tcc cca gct gac atc acc cat ccc act cca gcc cca ggc ccc tct			529
Pro Ser Pro Ala Asp Ile Thr His Pro Thr Pro Ala Pro Gly Pro Ser			
160	165	170	175
gcc cac gct gca ccc agc acc acc agc gcc ctg acc ccc gga cct gcc			577
Ala His Ala Ala Pro Ser Thr Thr Ser Ala Leu Thr Pro Gly Pro Ala			
	180	185	190
gcc gcc gct gcc gac gcc gca gct tcc tcc gtt gcc aag ggc ggg gct			625
Ala Ala Ala Ala Asp Ala Ala Ala Ser Ser Val Ala Lys Gly Gly Ala			
	195	200	205
tag agctcaaccc agacacctgc aggtgccgga agctgcgaag gtgacacatg			678
gcttttcaga ctgagcaggg tgacttgccct cagaggctat atcccagtgg gggaacaaag			738
aggagcctgg taaaaaa			755

&lt;210&gt; 22

&lt;211&gt; 207

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 22

Met Ser Pro Leu Leu Arg Arg Leu Leu Leu Ala Ala Leu Leu Gln Leu	
1 5 10 15	
Ala Pro Ala Gln Ala Pro Val Ser Gln Pro Asp Ala Pro Gly His Gln	
20 25 30	
Arg Lys Val Val Ser Trp Ile Asp Val Tyr Thr Arg Ala Thr Cys Gln	
35 40 45	
Pro Arg Glu Val Val Val Pro Leu Thr Val Glu Leu Met Gly Thr Val	
50 55 60	
Ala Lys Gln Leu Val Pro Ser Cys Val Thr Val Gln Arg Cys Gly Gly	
65 70 75 80	
Cys Cys Pro Asp Asp Gly Leu Glu Cys Val Pro Thr Gly Gln His Gln	
85 90 95	
Val Arg Met Gln Ile Leu Met Ile Arg Tyr Pro Ser Ser Gln Leu Gly	
100 105 110	

Glu Met Ser Leu Glu Glu His Ser Gln Cys Glu Cys Arg Pro Lys Lys  
 115 120 125

Lys Asp Ser Ala Val Lys Pro Asp Arg Ala Ala Thr Pro His His Arg  
 130 135 140

Pro Gln Pro Arg Ser Val Pro Gly Trp Asp Ser Ala Pro Gly Ala Pro  
 145 150 155 160

Ser Pro Ala Asp Ile Thr His Pro Thr Pro Ala Pro Gly Pro Ser Ala  
 165 170 175

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 Met His  
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Gly	Leu	Asp	Leu	Ser	Asp	Ala	Glu	Pro	Asp	Ala	Gly	Glu	Ala	Thr	Ala	
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Tyr	Ala	Ser	Lys	Asp	Leu	Glu	Glu	Gln	Leu	Arg	Ser	Val	Ser	Ser	Val	
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gat	gaa	ctc	atg	act	gta	ctc	tac	cca	gaa	tat	tgg	aaa	atg	tac	aag	597
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Cys	Gln	Leu	Arg	Lys	Gly	Gly	Trp	Gln	His	Asn	Arg	Glu	Gln	Ala	Asn	
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Asn	Thr	Glu	Ile	Leu	Lys	Ser	Ile	Asp	Asn	Glu	Trp	Arg	Lys	Thr	Gln	
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Cys	Met	Pro	Arg	Glu	Val	Cys	Ile	Asp	Val	Gly	Lys	Glu	Phe	Gly	Val	
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Ala	Thr	Asn	Thr	Phe	Phe	Lys	Pro	Pro	Cys	Val	Ser	Val	Tyr	Arg	Cys	
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Gly	Gly	Cys	Cys	Asn	Ser	Glu	Gly	Leu	Gln	Cys	Met	Asn	Thr	Ser	Thr	
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Ser	Tyr	Leu	Ser	Lys	Thr	Leu	Phe	Glu	Ile	Thr	Val	Pro	Leu	Ser	Gln	
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Cys	Met	Ser	Lys	Leu	Asp	Val	Tyr	Arg	Gln	Val	His	Ser	Ile	Ile	Arg	
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Arg	Ser	Leu	Pro	Ala	Thr	Leu	Pro	Gln	Cys	Gln	Ala	Ala	Asn	Lys	Thr	
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Cys	Pro	Thr	Asn	Tyr	Met	Trp	Asn	Asn	His	Ile	Cys	Arg	Cys	Leu	Ala	
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Gln	Glu	Asp	Phe	Met	Phe	Ser	Ser	Asp	Ala	Gly	Asp	Asp	Ser	Thr	Asp	
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Gly Phe His Asp Ile Cys Gly Pro Asn Lys Glu Leu Asp Glu Glu Thr	
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Cys Gln Cys Val Cys Arg Ala Gly Leu Arg Pro Ala Ser Cys Gly Pro	
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His Lys Glu Leu Asp Arg Asn Ser Cys Gln Cys Val Cys Lys Asn Lys	
310 315 320	
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Leu Phe Pro Ser Gln Cys Gly Ala Asn Arg Glu Phe Asp Glu Asn Thr	
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Cys Gln Cys Val Cys Lys Arg Thr Cys Pro Arg Asn Gln Pro Leu Asn	
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cct gga aaa tgt gcc tgt gaa tgt aca gaa agt cca cag aaa tgc ttg	1461
Pro Gly Lys Cys Ala Cys Glu Cys Thr Glu Ser Pro Gln Lys Cys Leu	
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Leu Lys Gly Lys Lys Phe His His Gln Thr Cys Ser Cys Tyr Arg Arg	
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Pro Cys Thr Asn Arg Gln Lys Ala Cys Glu Pro Gly Phe Ser Tyr Ser	
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Glu Glu Val Cys Arg Cys Val Pro Ser Tyr Trp Lys Arg Pro Gln Met	
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Ser	
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Thr Ala Tyr Ala Ser Lys Asp Leu Glu Glu Gln Leu Arg Ser Val Ser  
 50 55 60

Ser Val Asp Glu Leu Met Thr Val Leu Tyr Pro Glu Tyr Trp Lys Met  
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Tyr Lys Cys Gln Leu Arg Lys Gly Gly Trp Gln His Asn Arg Glu Gln  
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Ala Asn Leu Asn Ser Arg Thr Glu Glu Thr Ile Lys Phe Ala Ala Ala  
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His Tyr Asn Thr Glu Ile Leu Lys Ser Ile Asp Asn Glu Trp Arg Lys  
 115 120 125

Thr Gln Cys Met Pro Arg Glu Val Cys Ile Asp Val Gly Lys Glu Phe  
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Gly Val Ala Thr Asn Thr Phe Phe Lys Pro Pro Cys Val Ser Val Tyr  
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Arg Cys Gly Gly Cys Cys Asn Ser Glu Gly Leu Gln Cys Met Asn Thr  
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Ser Thr Ser Tyr Leu Ser Lys Thr Leu Phe Glu Ile Thr Val Pro Leu  
 180 185 190

Ser Gln Gly Pro Lys Pro Val Thr Ile Ser Phe Ala Asn His Thr Ser  
 195 200 205

Cys Arg Cys Met Ser Lys Leu Asp Val Tyr Arg Gln Val His Ser Ile  
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Ile Arg Arg Ser Leu Pro Ala Thr Leu Pro Gln Cys Gln Ala Ala Asn  
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Lys Thr Cys Pro Thr Asn Tyr Met Trp Asn Asn His Ile Cys Arg Cys  
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 Gly Pro His Lys Glu Leu Asp Arg Asn Ser Cys Gln Cys Val Cys Lys  
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&lt;210&gt; 25

&lt;211&gt; 2029

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (411)..(1475)

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cta tgg gat agc aac aaa tgt aaa tgt gtt ttg cag gag gaa aat cca Leu Trp Asp Ser Asn Lys Cys Lys Cys Val Leu Gln Glu Glu Asn Pro 230 235 240			1136
ctt gct gga aca gaa gac cac tct cat ctc cag gaa cca gct ctc tgt Leu Ala Gly Thr Glu Asp His Ser His Leu Gln Glu Pro Ala Leu Cys 245 250 255			1184
ggg cca cac atg atg ttt gac gaa gat cgt tgc gag tgt gtc tgt aaa Gly Pro His Met Met Phe Asp Glu Asp Arg Cys Glu Cys Val Cys Lys 260 265 270			1232
aca cca tgt ccc aaa gat cta atc cag cac ccc aaa aac tgc agt tgc Thr Pro Cys Pro Lys Asp Leu Ile Gln His Pro Lys Asn Cys Ser Cys 275 280 285 290			1280
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cca aag gag aaa agg gct gcc cag ggg ccc cac agc cga aag aat cct Pro Lys Glu Lys Arg Ala Ala Gln Gly Pro His Ser Arg Lys Asn Pro 340 345 350			1472
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<211> 354

<212> PRT

<213> Homo sapiens

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 35 40 45

Ser Leu Glu Glu Leu Leu Arg Ile Thr His Ser Glu Asp Trp Lys Leu  
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Trp Arg Cys Arg Leu Arg Leu Lys Ser Phe Thr Ser Met Asp Ser Arg  
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Ser Ala Ser His Arg Ser Thr Arg Phe Ala Ala Thr Phe Tyr Asp Ile  
 85 90 95

Glu Thr Leu Lys Val Ile Asp Glu Glu Trp Gln Arg Thr Gln Cys Ser  
 100 105 110

Pro Arg Glu Thr Cys Val Glu Val Ala Ser Glu Leu Gly Lys Ser Thr  
 115 120 125

Asn Thr Phe Phe Lys Pro Pro Cys Val Asn Val Phe Arg Cys Gly Gly  
 130 135 140

Cys Cys Asn Glu Glu Ser Leu Ile Cys Met Asn Thr Ser Thr Ser Tyr  
 145 150 155 160

Ile Ser Lys Gln Leu Phe Glu Ile Ser Val Pro Leu Thr Ser Val Pro  
 165 170 175

Glu Leu Val Pro Val Lys Val Ala Asn His Thr Gly Cys Lys Cys Leu

180

185

190

Pro Thr Ala Pro Arg His Pro Tyr Ser Ile Ile Arg Arg Ser Ile Gln  
 195 200 205

Ile Pro Glu Glu Asp Arg Cys Ser His Ser Lys Lys Leu Cys Pro Ile  
 210 215 220

Asp Met Leu Trp Asp Ser Asn Lys Cys Lys Cys Val Leu Gln Glu Glu  
 225 230 235 240

Asn Pro Leu Ala Gly Thr Glu Asp His Ser His Leu Gln Glu Pro Ala  
 245 250 255

Leu Cys Gly Pro His Met Met Phe Asp Glu Asp Arg Cys Glu Cys Val  
 260 265 270

Cys Lys Thr Pro Cys Pro Lys Asp Leu Ile Gln His Pro Lys Asn Cys  
 275 280 285

Ser Cys Phe Glu Cys Lys Glu Ser Leu Glu Thr Cys Cys Gln Lys His  
 290 295 300

Lys Leu Phe His Pro Asp Thr Cys Ser Cys Glu Asp Arg Cys Pro Phe  
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His Thr Arg Pro Cys Ala Ser Gly Lys Thr Ala Cys Ala Lys His Cys  
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Arg Phe Pro Lys Glu Lys Arg Ala Ala Gln Gly Pro His Ser Arg Lys  
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<222> (322)..(771)





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Arg Ser Tyr Cys Arg Ala Leu Glu Arg Leu Val Asp Val Val Ser Glu  
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Tyr Pro Ser Glu Val Glu His Met Phe Ser Pro Ser Cys Val Ser Leu  
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Leu Arg Cys Thr Gly Cys Cys Gly Asp Glu Asn Leu His Cys Val Pro  
85 90 95

Val Glu Thr Ala Asn Val Thr Met Gln Leu Leu Lys Ile Arg Ser Gly  
100 105 110

Asp Arg Pro Ser Tyr Val Glu Leu Thr Phe Ser Gln His Val Arg Cys  
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Ala Val Pro Arg Arg  
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<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (304)..(4374)

<400> 29

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agg atg cag agc aag gtg ctg ctg gcc gtc gcc ctg tgg ctc tgc gtg      348
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Glu Thr Arg Ala Ala Ser Val Gly Leu Pro Ser Val Ser Leu Asp Leu
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Pro Arg Leu Ser Ile Gln Lys Asp Ile Leu Thr Ile Lys Ala Asn Thr
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act ctt caa att act tgc agg gga cag agg gac ttg gac tgg ctt tgg      492
Thr Leu Gln Ile Thr Cys Arg Gly Gln Arg Asp Leu Asp Trp Leu Trp
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ccc aat aat cag agt ggc agt gag caa agg gtg gag gtg act gag tgc      540
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Ser	Val	Ile	Tyr	Val	Tyr	Val	Gln	Asp	Tyr	Arg	Ser	Pro	Phe	Ile	Ala	
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Ser	Val	Ser	Asp	Gln	His	Gly	Val	Val	Tyr	Ile	Thr	Glu	Asn	Lys	Asn	
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Lys	Thr	Val	Val	Ile	Pro	Cys	Leu	Gly	Ser	Ile	Ser	Asn	Leu	Asn	Val	
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Arg	Ile	Ser	Trp	Asp	Ser	Lys	Lys	Gly	Phe	Thr	Ile	Pro	Ser	Tyr	Met	
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Ile	Ser	Tyr	Ala	Gly	Met	Val	Phe	Cys	Glu	Ala	Lys	Ile	Asn	Asp	Glu	
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Glu	Lys	Leu	Val	Leu	Asn	Cys	Thr	Ala	Arg	Thr	Glu	Leu	Asn	Val	Gly	
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Ile	Asp	Phe	Asn	Trp	Glu	Tyr	Pro	Ser	Ser	Lys	His	Gln	His	Lys	Lys	
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Leu	Val	Asn	Arg	Asp	Leu	Lys	Thr	Gln	Ser	Gly	Ser	Glu	Met	Lys	Lys	
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Phe	Leu	Ser	Thr	Leu	Thr	Ile	Asp	Gly	Val	Thr	Arg	Ser	Asp	Gln	Gly	
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Thr	Phe	Val	Arg	Val	His	Glu	Lys	Pro	Phe	Val	Ala	Phe	Gly	Ser	Gly	
					325					330					335	
atg	gaa	tct	ctg	gtg	gaa	gcc	acg	gtg	ggg	gag	cgt	gtc	aga	atc	cct	1356
Met	Glu	Ser	Leu	Val	Glu	Ala	Thr	Val	Gly	Glu	Arg	Val	Arg	Ile	Pro	

				340				345				350				
gcg	aag	tac	ctt	ggt	tac	cca	ccc	cca	gaa	ata	aaa	tgg	tat	aaa	aat	1404
Ala	Lys	Tyr	Leu	Gly	Tyr	Pro	Pro	Pro	Glu	Ile	Lys	Trp	Tyr	Lys	Asn	
			355				360				365					
gga	ata	ccc	ctt	gag	tcc	aat	cac	aca	att	aaa	gcg	ggg	cat	gta	ctg	1452
Gly	Ile	Pro	Leu	Glu	Ser	Asn	His	Thr	Ile	Lys	Ala	Gly	His	Val	Leu	
			370				375				380					
acg	att	atg	gaa	gtg	agt	gaa	aga	gac	aca	gga	aat	tac	act	gtc	atc	1500
Thr	Ile	Met	Glu	Val	Ser	Glu	Arg	Asp	Thr	Gly	Asn	Tyr	Thr	Val	Ile	
			385				390				395					
ctt	acc	aat	ccc	att	tca	aag	gag	aag	cag	agc	cat	gtg	gtc	tct	ctg	1548
Leu	Thr	Asn	Pro	Ile	Ser	Lys	Glu	Lys	Gln	Ser	His	Val	Val	Ser	Leu	
400				405				410				415				
gtt	gtg	tat	gtc	cca	ccc	cag	att	ggt	gag	aaa	tct	cta	atc	tct	cct	1596
Val	Val	Tyr	Val	Pro	Pro	Gln	Ile	Gly	Glu	Lys	Ser	Leu	Ile	Ser	Pro	
			420				425				430					
gtg	gat	tcc	tac	cag	tac	ggc	acc	act	caa	acg	ctg	aca	tgt	acg	gtc	1644
Val	Asp	Ser	Tyr	Gln	Tyr	Gly	Thr	Thr	Gln	Thr	Leu	Thr	Cys	Thr	Val	
			435				440				445					
tat	gcc	att	cct	ccc	ccg	cat	cac	atc	cac	tgg	tat	tgg	cag	ttg	gag	1692
Tyr	Ala	Ile	Pro	Pro	Pro	His	His	Ile	His	Trp	Tyr	Trp	Gln	Leu	Glu	
			450				455				460					
gaa	gag	tgc	gcc	aac	gag	ccc	agc	caa	gct	gtc	tca	gtg	aca	aac	cca	1740
Glu	Glu	Cys	Ala	Asn	Glu	Pro	Ser	Gln	Ala	Val	Ser	Val	Thr	Asn	Pro	
			465				470				475					
tac	cct	tgt	gaa	gaa	tgg	aga	agt	gtg	gag	gac	ttc	cag	gga	gga	aat	1788
Tyr	Pro	Cys	Glu	Glu	Trp	Arg	Ser	Val	Glu	Asp	Phe	Gln	Gly	Gly	Asn	
480				485				490				495				
aaa	att	gaa	gtt	aat	aaa	aat	caa	ttt	gct	cta	att	gaa	gga	aaa	aac	1836
Lys	Ile	Glu	Val	Asn	Lys	Asn	Gln	Phe	Ala	Leu	Ile	Glu	Gly	Lys	Asn	
			500				505				510					
aaa	act	gta	agt	acc	ctt	gtt	atc	caa	gcg	gca	aat	gtg	tca	gct	ttg	1884
Lys	Thr	Val	Ser	Thr	Leu	Val	Ile	Gln	Ala	Ala	Asn	Val	Ser	Ala	Leu	
			515				520				525					
tac	aaa	tgt	gaa	gcg	gtc	aac	aaa	gtc	ggg	aga	gga	gag	agg	gtg	atc	1932
Tyr	Lys	Cys	Glu	Ala	Val	Asn	Lys	Val	Gly	Arg	Gly	Glu	Arg	Val	Ile	
			530				535				540					
tcc	ttc	cac	gtg	acc	agg	ggt	cct	gaa	att	act	ttg	caa	cct	gac	atg	1980
Ser	Phe	His	Val	Thr	Arg	Gly	Pro	Glu	Ile	Thr	Leu	Gln	Pro	Asp	Met	
			545				550				555					
cag	ccc	act	gag	cag	gag	agc	gtg	tct	ttg	tgg	tgc	act	gca	gac	aga	2028
Gln	Pro	Thr	Glu	Gln	Glu	Ser	Val	Ser	Leu	Trp	Cys	Thr	Ala	Asp	Arg	
560				565				570				575				
tct	acg	ttt	gag	aac	ctc	aca	tgg	tac	aag	ctt	ggc	cca	cag	cct	ctg	2076
Ser	Thr	Phe	Glu	Asn	Leu	Thr	Trp	Tyr	Lys	Leu	Gly	Pro	Gln	Pro	Leu	
			580				585				590					

cca atc cat gtg gga gag ttg ccc aca cct gtt tgc aag aac ttg gat Pro Ile His Val Gly Glu Leu Pro Thr Pro Val Cys Lys Asn Leu Asp 595 600 605	2124
act ctt tgg aaa ttg aat gcc acc atg ttc tct aat agc aca aat gac Thr Leu Trp Lys Leu Asn Ala Thr Met Phe Ser Asn Ser Thr Asn Asp 610 615 620	2172
att ttg atc atg gag ctt aag aat gca tcc ttg cag gac caa gga gac Ile Leu Ile Met Glu Leu Lys Asn Ala Ser Leu Gln Asp Gln Gly Asp 625 630 635	2220
tat gtc tgc ctt gct caa gac agg aag acc aag aaa aga cat tgc gtg Tyr Val Cys Leu Ala Gln Asp Arg Lys Thr Lys Lys Arg His Cys Val 640 645 650 655	2268
gtc agg cag ctc aca gtc cta gag cgt gtg gca ccc acg atc aca gga Val Arg Gln Leu Thr Val Leu Glu Arg Val Ala Pro Thr Ile Thr Gly 660 665 670	2316
aac ctg gag aat cag acg aca agt att ggg gaa agc atc gaa gtc tca Asn Leu Glu Asn Gln Thr Thr Ser Ile Gly Glu Ser Ile Glu Val Ser 675 680 685	2364
tgc acg gca tct ggg aat ccc cct cca cag atc atg tgg ttt aaa gat Cys Thr Ala Ser Gly Asn Pro Pro Pro Gln Ile Met Trp Phe Lys Asp 690 695 700	2412
aat gag acc ctt gta gaa gac tca ggc att gta ttg aag gat ggg aac Asn Glu Thr Leu Val Glu Asp Ser Gly Ile Val Leu Lys Asp Gly Asn 705 710 715	2460
cgg aac ctc act atc cgc aga gtg agg aag gag gac gaa ggc ctc tac Arg Asn Leu Thr Ile Arg Arg Val Arg Lys Glu Asp Glu Gly Leu Tyr 720 725 730 735	2508
acc tgc cag gca tgc agt gtt ctt ggc tgt gca aaa gtg gag gca ttt Thr Cys Gln Ala Cys Ser Val Leu Gly Cys Ala Lys Val Glu Ala Phe 740 745 750	2556
ttc ata ata gaa ggt gcc cag gaa aag acg aac ttg gaa atc att att Phe Ile Ile Glu Gly Ala Gln Glu Lys Thr Asn Leu Glu Ile Ile Ile 755 760 765	2604
cta gta ggc acg gcg gtg att gcc atg ttc ttc tgg cta ctt ctt gtc Leu Val Gly Thr Ala Val Ile Ala Met Phe Phe Trp Leu Leu Leu Val 770 775 780	2652
atc atc cta cgg acc gtt aag cgg gcc aat gga ggg gaa ctg aag aca Ile Ile Leu Arg Thr Val Lys Arg Ala Asn Gly Gly Glu Leu Lys Thr 785 790 795	2700
ggc tac ttg tcc atc gtc atg gat cca gat gaa ctc cca ttg gat gaa Gly Tyr Leu Ser Ile Val Met Asp Pro Asp Glu Leu Pro Leu Asp Glu 800 805 810 815	2748
cat tgt gaa cga ctg cct tat gat gcc agc aaa tgg gaa ttc ccc aga His Cys Glu Arg Leu Pro Tyr Asp Ala Ser Lys Trp Glu Phe Pro Arg 820 825 830	2796
gac cgg ctg aag cta ggt aag cct ctt ggc cgt ggt gcc ttt ggc caa	2844

Asp	Arg	Leu	Lys	Leu	Gly	Lys	Pro	Leu	Gly	Arg	Gly	Ala	Phe	Gly	Gln	
		835						840					845			
gtg	att	gaa	gca	gat	gcc	ttt	gga	att	gac	aag	aca	gca	act	tgc	agg	2892
Val	Ile	Glu	Ala	Asp	Ala	Phe	Gly	Ile	Asp	Lys	Thr	Ala	Thr	Cys	Arg	
		850					855					860				
aca	gta	gca	gtc	aaa	atg	ttg	aaa	gaa	gga	gca	aca	cac	agt	gag	cat	2940
Thr	Val	Ala	Val	Lys	Met	Leu	Lys	Glu	Gly	Ala	Thr	His	Ser	Glu	His	
	865					870					875					
cga	gct	ctc	atg	tct	gaa	ctc	aag	atc	ctc	att	cat	att	ggt	cac	cat	2988
Arg	Ala	Leu	Met	Ser	Glu	Leu	Lys	Ile	Leu	Ile	His	Ile	Gly	His	His	
	880				885					890					895	
ctc	aat	gtg	gtc	aac	ctt	cta	ggt	gcc	tgt	acc	aag	cca	gga	ggg	cca	3036
Leu	Asn	Val	Val	Asn	Leu	Leu	Gly	Ala	Cys	Thr	Lys	Pro	Gly	Gly	Pro	
				900					905						910	
ctc	atg	gtg	att	gtg	gaa	ttc	tgc	aaa	ttt	gga	aac	ctg	tcc	act	tac	3084
Leu	Met	Val	Ile	Val	Glu	Phe	Cys	Lys	Phe	Gly	Asn	Leu	Ser	Thr	Tyr	
		915						920					925			
ctg	agg	agc	aag	aga	aat	gaa	ttt	gtc	ccc	tac	aag	acc	aaa	ggg	gca	3132
Leu	Arg	Ser	Lys	Arg	Asn	Glu	Phe	Val	Pro	Tyr	Lys	Thr	Lys	Gly	Ala	
		930					935					940				
cga	ttc	cgt	caa	ggg	aaa	gac	tac	gtt	gga	gca	atc	cct	gtg	gat	ctg	3180
Arg	Phe	Arg	Gln	Gly	Lys	Asp	Tyr	Val	Gly	Ala	Ile	Pro	Val	Asp	Leu	
	945					950					955					
aaa	cgg	cgc	ttg	gac	agc	atc	acc	agt	agc	cag	agc	tca	gcc	agc	tct	3228
Lys	Arg	Arg	Leu	Asp	Ser	Ile	Thr	Ser	Ser	Gln	Ser	Ser	Ala	Ser	Ser	
	960				965					970					975	
gga	ttt	gtg	gag	gag	aag	tcc	ctc	agt	gat	gta	gaa	gaa	gag	gaa	gct	3276
Gly	Phe	Val	Glu	Glu	Lys	Ser	Leu	Ser	Asp	Val	Glu	Glu	Glu	Glu	Ala	
				980					985						990	
cct	gaa	gat	ctg	tat	aag	gac	ttc	ctg	acc	ttg	gag	cat	ctc	atc	tgt	3324
Pro	Glu	Asp	Leu	Tyr	Lys	Asp	Phe	Leu	Thr	Leu	Glu	His	Leu	Ile	Cys	
			995					1000						1005		
tac	agc	ttc	caa	gtg	gct	aag	ggc	atg	gag	ttc	ttg	gca	tcg	cga		3369
Tyr	Ser	Phe	Gln	Val	Ala	Lys	Gly	Met	Glu	Phe	Leu	Ala	Ser	Arg		
		1010					1015					1020				
aag	tgt	atc	cac	agg	gac	ctg	gcg	gca	cga	aat	atc	ctc	tta	tcg		3414
Lys	Cys	Ile	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Ile	Leu	Leu	Ser		
		1025					1030					1035				
gag	aag	aac	gtg	gtt	aaa	atc	tgt	gac	ttt	ggc	ttg	gcc	cgg	gat		3459
Glu	Lys	Asn	Val	Val	Lys	Ile	Cys	Asp	Phe	Gly	Leu	Ala	Arg	Asp		
		1040					1045					1050				
att	tat	aaa	gat	cca	gat	tat	gtc	aga	aaa	gga	gat	gct	cgc	ctc		3504
Ile	Tyr	Lys	Asp	Pro	Asp	Tyr	Val	Arg	Lys	Gly	Asp	Ala	Arg	Leu		
		1055					1060					1065				
cct	ttg	aaa	tgg	atg	gcc	cca	gaa	aca	att	ttt	gac	aga	gtg	tac		3549
Pro	Leu	Lys	Trp	Met	Ala	Pro	Glu	Thr	Ile	Phe	Asp	Arg	Val	Tyr		

1070	1075	1080	
aca atc cag agt gac gtc tgg tct Thr Ile Gln Ser Asp Val Trp	tct Ser 1090	ttt ggt gtt ttg ctg tgg gaa Phe Gly Val Leu Leu Trp Glu	3594
1085		1095	
ata ttt tcc tta ggt gct tct cca Ile Phe Ser Leu Gly Ala Ser Pro	tat cct ggg gta aag att gat Tyr Pro Gly Val Lys Ile Asp	3639	
1100	1105	1110	
gaa gaa ttt tgt agg cga ttg aaa Glu Glu Phe Cys Arg Arg Leu Lys	gaa gga act aga atg agg gcc Glu Gly Thr Arg Met Arg Ala	3684	
1115	1120	1125	
cct gat tat act aca cca gaa atg Pro Asp Tyr Thr Thr Pro Glu Met	tac cag acc atg ctg gac tgc Tyr Gln Thr Met Leu Asp Cys	3729	
1130	1135	1140	
tgg cac ggg gag ccc agt cag aga Trp His Gly Glu Pro Ser Gln Arg	ccc acg ttt tca gag ttg gtg Pro Thr Phe Ser Glu Leu Val	3774	
1145	1150	1155	
gaa cat ttg gga aat ctc ttg caa Glu His Leu Gly Asn Leu Leu Gln	gct aat gct cag cag gat ggc Ala Asn Ala Gln Gln Asp Gly	3819	
1160	1165	1170	
aaa gac tac att gtt ctt ccg ata Lys Asp Tyr Ile Val Leu Pro Ile	tca gag act ttg agc atg gaa Ser Glu Thr Leu Ser Met Glu	3864	
1175	1180	1185	
gag gat tct gga ctc tct ctg cct Glu Asp Ser Gly Leu Ser Leu Pro	acc tca cct gtt tcc tgt atg Thr Ser Pro Val Ser Cys Met	3909	
1190	1195	1200	
gag gag gag gaa gta tgt gac ccc Glu Glu Glu Glu Val Cys Asp Pro	aaa ttc cat tat gac aac aca Lys Phe His Tyr Asp Asn Thr	3954	
1205	1210	1215	
gca gga atc agt cag tat ctg cag Ala Gly Ile Ser Gln Tyr Leu Gln	aac agt aag cga aag agc cgg Asn Ser Lys Arg Lys Ser Arg	3999	
1220	1225	1230	
cct gtg agt gta aaa aca ttt gaa Pro Val Ser Val Lys Thr Phe Glu	gat atc ccg tta gaa gaa cca Asp Ile Pro Leu Glu Glu Pro	4044	
1235	1240	1245	
gaa gta aaa gta atc cca gat gac Glu Val Lys Val Ile Pro Asp Asp	aac cag acg gac agt ggt atg Asn Gln Thr Asp Ser Gly Met	4089	
1250	1255	1260	
gtt ctt gcc tca gaa gag ctg aaa Val Leu Ala Ser Glu Glu Leu Lys	act ttg gaa gac aga acc aaa Thr Leu Glu Asp Arg Thr Lys	4134	
1265	1270	1275	
tta tct cca tct ttt ggt gga atg Leu Ser Pro Ser Phe Gly Gly Met	gtg ccc agc aaa agc agg gag Val Pro Ser Lys Ser Arg Glu	4179	
1280	1285	1290	
tct gtg gca tct gaa ggc tca aac Ser Val Ala Ser Glu Gly Ser Asn	cag aca agc ggc tac cag tcc Gln Thr Ser Gly Tyr Gln Ser	4224	
1295	1300	1305	



gga tat cac tcc gat gac aca gac	acc acc gtg tac tcc	agt gag	4269
Gly Tyr His Ser Asp Asp Thr Asp	Thr Thr Val Tyr Ser	Ser Glu	
1310	1315	1320	
gaa gca gaa ctt tta aag ctg ata	gag att gga gtg caa	acc ggt	4314
Glu Ala Glu Leu Leu Lys Leu Ile	Glu Ile Gly Val Gln	Thr Gly	
1325	1330	1335	
agc aca gcc cag att ctc cag cct	gac tcg ggg acc aca	ctg agc	4359
Ser Thr Ala Gln Ile Leu Gln Pro	Asp Ser Gly Thr Thr	Leu Ser	
1340	1345	1350	
tct cct cct gtt taa aaggaagcat	ccacacccca actcccggac	atcacatgag	4414
Ser Pro Pro Val			
1355			
aggtctgctc agattttgaa gtgttggttct	ttccaccagc aggaagtagc	cgcatttgat	4474
tttcatttcg acaacagaaa aaggacctcg	gactgcaggg agccagtctt	ctaggcatat	4534
cctggaagag gcttgtagacc caagaatgtg	tctgtgtctt ctcccagtgt	tgacctgatc	4594
ctctttttttc attcatttaa aaagcattat	catgcccctg ctgcgggtct	caccatgggt	4654
ttagaacaaa gagcttcaag caatggcccc	atcctcaaag aagtagcagt	acctggggag	4714
ctgacacttc tgtaaaacta gaagataaac	caggcaacgt aagtgttcga	ggtgttgaa	4774
atgggaagga tttgcagggc tgagtctatc	caagaggctt tgtttaggac	gtgggtccca	4834
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ccaacccact ctcaccccgcc aaccatcag	tatttttagtt atttggcctc	tactccagta	5434
aacctgattg ggtttgttca ctctctgaat	gattattagc cagacttcaa	aattatttta	5494
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ctgatttttg cccttggtct gtcctttttt	tcaaaaaaga aaatgtgttt	tttgtttggt	5614
accatagtgt gaaatgctgg gaacaatgac	tataagacat gctatggcac	atatatttat	5674
agtctgttta tgtagaaaca aatgtaatat	attaaagcct tatatataat	gaactttgta	5734
ctattcacat tttgtatcag tattatgtag	cataacaaag gtcataatgc	tttcagcaat	5794
tgatgtcatt ttattaaaga acattgaaaa	acttga		5830

&lt;210&gt; 30

&lt;211&gt; 1356

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 30

Met Gln Ser Lys Val Leu Leu Ala Val Ala Leu Trp Leu Cys Val Glu  
 1 5 10 15

Thr Arg Ala Ala Ser Val Gly Leu Pro Ser Val Ser Leu Asp Leu Pro  
 20 25 30

Arg Leu Ser Ile Gln Lys Asp Ile Leu Thr Ile Lys Ala Asn Thr Thr  
 35 40 45

Leu Gln Ile Thr Cys Arg Gly Gln Arg Asp Leu Asp Trp Leu Trp Pro  
 50 55 60

Asn Asn Gln Ser Gly Ser Glu Gln Arg Val Glu Val Thr Glu Cys Ser  
 65 70 75 80

Asp Gly Leu Phe Cys Lys Thr Leu Thr Ile Pro Lys Val Ile Gly Asn  
 85 90 95

Asp Thr Gly Ala Tyr Lys Cys Phe Tyr Arg Glu Thr Asp Leu Ala Ser  
 100 105 110

Val Ile Tyr Val Tyr Val Gln Asp Tyr Arg Ser Pro Phe Ile Ala Ser  
 115 120 125

Val Ser Asp Gln His Gly Val Val Tyr Ile Thr Glu Asn Lys Asn Lys  
 130 135 140

Thr Val Val Ile Pro Cys Leu Gly Ser Ile Ser Asn Leu Asn Val Ser  
 145 150 155 160

Leu Cys Ala Arg Tyr Pro Glu Lys Arg Phe Val Pro Asp Gly Asn Arg  
 165 170 175

Ile Ser Trp Asp Ser Lys Lys Gly Phe Thr Ile Pro Ser Tyr Met Ile  
 180 185 190

Ser Tyr Ala Gly Met Val Phe Cys Glu Ala Lys Ile Asn Asp Glu Ser  
 195 200 205

Tyr Gln Ser Ile Met Tyr Ile Val Val Val Val Gly Tyr Arg Ile Tyr  
 210 215 220  
 Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu  
 225 230 235 240  
 Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile  
 245 250 255  
 Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu  
 260 265 270  
 Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe  
 275 280 285  
 Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu  
 290 295 300  
 Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr  
 305 310 315 320  
 Phe Val Arg Val His Glu Lys Pro Phe Val Ala Phe Gly Ser Gly Met  
 325 330 335  
 Glu Ser Leu Val Glu Ala Thr Val Gly Glu Arg Val Arg Ile Pro Ala  
 340 345 350  
 Lys Tyr Leu Gly Tyr Pro Pro Pro Glu Ile Lys Trp Tyr Lys Asn Gly  
 355 360 365  
 Ile Pro Leu Glu Ser Asn His Thr Ile Lys Ala Gly His Val Leu Thr  
 370 375 380  
 Ile Met Glu Val Ser Glu Arg Asp Thr Gly Asn Tyr Thr Val Ile Leu  
 385 390 395 400  
 Thr Asn Pro Ile Ser Lys Glu Lys Gln Ser His Val Val Ser Leu Val  
 405 410 415  
 Val Tyr Val Pro Pro Gln Ile Gly Glu Lys Ser Leu Ile Ser Pro Val  
 420 425 430  
 Asp Ser Tyr Gln Tyr Gly Thr Thr Gln Thr Leu Thr Cys Thr Val Tyr  
 435 440 445  
 Ala Ile Pro Pro Pro His His Ile His Trp Tyr Trp Gln Leu Glu Glu  
 450 455 460

Glu Cys Ala Asn Glu Pro Ser Gln Ala Val Ser Val Thr Asn Pro Tyr  
 465 470 475 480

Pro Cys Glu Glu Trp Arg Ser Val Glu Asp Phe Gln Gly Gly Asn Lys  
 485 490 495

Ile Glu Val Asn Lys Asn Gln Phe Ala Leu Ile Glu Gly Lys Asn Lys  
 500 505 510

Thr Val Ser Thr Leu Val Ile Gln Ala Ala Asn Val Ser Ala Leu Tyr  
 515 520 525

Lys Cys Glu Ala Val Asn Lys Val Gly Arg Gly Glu Arg Val Ile Ser  
 530 535 540

Phe His Val Thr Arg Gly Pro Glu Ile Thr Leu Gln Pro Asp Met Gln  
 545 550 555 560

Pro Thr Glu Gln Glu Ser Val Ser Leu Trp Cys Thr Ala Asp Arg Ser  
 565 570 575

Thr Phe Glu Asn Leu Thr Trp Tyr Lys Leu Gly Pro Gln Pro Leu Pro  
 580 585 590

Ile His Val Gly Glu Leu Pro Thr Pro Val Cys Lys Asn Leu Asp Thr  
 595 600 605

Leu Trp Lys Leu Asn Ala Thr Met Phe Ser Asn Ser Thr Asn Asp Ile  
 610 615 620

Leu Ile Met Glu Leu Lys Asn Ala Ser Leu Gln Asp Gln Gly Asp Tyr  
 625 630 635 640

Val Cys Leu Ala Gln Asp Arg Lys Thr Lys Lys Arg His Cys Val Val  
 645 650 655

Arg Gln Leu Thr Val Leu Glu Arg Val Ala Pro Thr Ile Thr Gly Asn  
 660 665 670

Leu Glu Asn Gln Thr Thr Ser Ile Gly Glu Ser Ile Glu Val Ser Cys  
 675 680 685

Thr Ala Ser Gly Asn Pro Pro Pro Gln Ile Met Trp Phe Lys Asp Asn  
 690 695 700

Glu Thr Leu Val Glu Asp Ser Gly Ile Val Leu Lys Asp Gly Asn Arg  
 705 710 715 720

Asn Leu Thr Ile Arg Arg Val Arg Lys Glu Asp Glu Gly Leu Tyr Thr  
 725 730 735

Cys Gln Ala Cys Ser Val Leu Gly Cys Ala Lys Val Glu Ala Phe Phe  
 740 745 750

Ile Ile Glu Gly Ala Gln Glu Lys Thr Asn Leu Glu Ile Ile Ile Leu  
 755 760 765

Val Gly Thr Ala Val Ile Ala Met Phe Phe Trp Leu Leu Leu Val Ile  
 770 775 780

Ile Leu Arg Thr Val Lys Arg Ala Asn Gly Gly Glu Leu Lys Thr Gly  
 785 790 795 800

Tyr Leu Ser Ile Val Met Asp Pro Asp Glu Leu Pro Leu Asp Glu His  
 805 810 815

Cys Glu Arg Leu Pro Tyr Asp Ala Ser Lys Trp Glu Phe Pro Arg Asp  
 820 825 830

Arg Leu Lys Leu Gly Lys Pro Leu Gly Arg Gly Ala Phe Gly Gln Val  
 835 840 845

Ile Glu Ala Asp Ala Phe Gly Ile Asp Lys Thr Ala Thr Cys Arg Thr  
 850 855 860

Val Ala Val Lys Met Leu Lys Glu Gly Ala Thr His Ser Glu His Arg  
 865 870 875 880

Ala Leu Met Ser Glu Leu Lys Ile Leu Ile His Ile Gly His His Leu  
 885 890 895

Asn Val Val Asn Leu Leu Gly Ala Cys Thr Lys Pro Gly Gly Pro Leu  
 900 905 910

Met Val Ile Val Glu Phe Cys Lys Phe Gly Asn Leu Ser Thr Tyr Leu  
 915 920 925

Arg Ser Lys Arg Asn Glu Phe Val Pro Tyr Lys Thr Lys Gly Ala Arg  
 930 935 940

Phe Arg Gln Gly Lys Asp Tyr Val Gly Ala Ile Pro Val Asp Leu Lys  
 945 950 955 960

Arg Arg Leu Asp Ser Ile Thr Ser Ser Gln Ser Ser Ala Ser Ser Gly

965

970

975

Phe Val Glu Glu Lys Ser Leu Ser Asp Val Glu Glu Glu Glu Ala Pro  
 980 985 990

Glu Asp Leu Tyr Lys Asp Phe Leu Thr Leu Glu His Leu Ile Cys Tyr  
 995 1000 1005

Ser Phe Gln Val Ala Lys Gly Met Glu Phe Leu Ala Ser Arg Lys  
 1010 1015 1020

Cys Ile His Arg Asp Leu Ala Ala Arg Asn Ile Leu Leu Ser Glu  
 1025 1030 1035

Lys Asn Val Val Lys Ile Cys Asp Phe Gly Leu Ala Arg Asp Ile  
 1040 1045 1050

Tyr Lys Asp Pro Asp Tyr Val Arg Lys Gly Asp Ala Arg Leu Pro  
 1055 1060 1065

Leu Lys Trp Met Ala Pro Glu Thr Ile Phe Asp Arg Val Tyr Thr  
 1070 1075 1080

Ile Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile  
 1085 1090 1095

Phe Ser Leu Gly Ala Ser Pro Tyr Pro Gly Val Lys Ile Asp Glu  
 1100 1105 1110

Glu Phe Cys Arg Arg Leu Lys Glu Gly Thr Arg Met Arg Ala Pro  
 1115 1120 1125

Asp Tyr Thr Thr Pro Glu Met Tyr Gln Thr Met Leu Asp Cys Trp  
 1130 1135 1140

His Gly Glu Pro Ser Gln Arg Pro Thr Phe Ser Glu Leu Val Glu  
 1145 1150 1155

His Leu Gly Asn Leu Leu Gln Ala Asn Ala Gln Gln Asp Gly Lys  
 1160 1165 1170

Asp Tyr Ile Val Leu Pro Ile Ser Glu Thr Leu Ser Met Glu Glu  
 1175 1180 1185

Asp Ser Gly Leu Ser Leu Pro Thr Ser Pro Val Ser Cys Met Glu  
 1190 1195 1200

Glu Glu Glu Val Cys Asp Pro Lys Phe His Tyr Asp Asn Thr Ala  
 1205 1210 1215  
 Gly Ile Ser Gln Tyr Leu Gln Asn Ser Lys Arg Lys Ser Arg Pro  
 1220 1225 1230  
 Val Ser Val Lys Thr Phe Glu Asp Ile Pro Leu Glu Glu Pro Glu  
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 Val Lys Val Ile Pro Asp Asp Asn Gln Thr Asp Ser Gly Met Val  
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 Leu Ala Ser Glu Glu Leu Lys Thr Leu Glu Asp Arg Thr Lys Leu  
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 Ser Pro Ser Phe Gly Gly Met Val Pro Ser Lys Ser Arg Glu Ser  
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 Tyr His Ser Asp Asp Thr Asp Thr Thr Val Tyr Ser Ser Glu Glu  
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 Thr Ala Gln Ile Leu Gln Pro Asp Ser Gly Thr Thr Leu Ser Ser  
 1340 1345 1350  
 Pro Pro Val  
 1355

&lt;210&gt; 31

&lt;211&gt; 4195

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (20)..(3913)

&lt;400&gt; 31

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 Met Gln Arg Gly Ala Ala Leu Cys Leu Arg Leu

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Trp	Leu	Cys	Leu	Gly	Leu	Leu	Asp	Gly	Leu	Val	Ser	Gly	Tyr	Ser	Met				
				15					20					25					
acc	ccc	ccg	acc	ttg	aac	atc	acg	gag	gag	tca	cac	gtc	atc	gac	acc	148			
Thr	Pro	Pro	Thr	Leu	Asn	Ile	Thr	Glu	Glu	Ser	His	Val	Ile	Asp	Thr				
				30					35					40					
ggt	gac	agc	ctg	tcc	atc	tcc	tgc	agg	gga	cag	cac	ccc	ctc	gag	tgg	196			
Gly	Asp	Ser	Leu	Ser	Ile	Ser	Cys	Arg	Gly	Gln	His	Pro	Leu	Glu	Trp				
				45					50					55					
gct	tgg	cca	gga	gct	cag	gag	gcg	cca	gcc	acc	gga	gac	aag	gac	agc	244			
Ala	Trp	Pro	Gly	Ala	Gln	Glu	Ala	Pro	Ala	Thr	Gly	Asp	Lys	Asp	Ser				
				60					65					70					
gag	gac	acg	ggg	gtg	gtg	cga	gac	tgc	gag	ggc	aca	gac	gcc	agg	ccc	292			
Glu	Asp	Thr	Gly	Val	Val	Arg	Asp	Cys	Glu	Gly	Thr	Asp	Ala	Arg	Pro				
				80					85					90					
tac	tgc	aag	gtg	ttg	ctg	ctg	cac	gag	gta	cat	gcc	aac	gac	aca	ggc	340			
Tyr	Cys	Lys	Val	Leu	Leu	Leu	His	Glu	Val	His	Ala	Asn	Asp	Thr	Gly				
				95					100					105					
agc	tac	gtc	tgc	tac	tac	aag	tac	atc	aag	gca	cgc	atc	gag	ggc	acc	388			
Ser	Tyr	Val	Cys	Tyr	Tyr	Lys	Tyr	Ile	Lys	Ala	Arg	Ile	Glu	Gly	Thr				
				110					115					120					
acg	gcc	gcc	agc	tcc	tac	gtg	ttc	gtg	aga	gac	ttt	gag	cag	cca	ttc	436			
Thr	Ala	Ala	Ser	Ser	Tyr	Val	Phe	Val	Arg	Asp	Phe	Glu	Gln	Pro	Phe				
				125					130					135					
atc	aac	aag	cct	gac	acg	ctc	ttg	gtc	aac	agg	aag	gac	gcc	atg	tgg	484			
Ile	Asn	Lys	Pro	Asp	Thr	Leu	Leu	Val	Asn	Arg	Lys	Asp	Ala	Met	Trp				
				140					145					150					
gtg	ccc	tgt	ctg	gtg	tcc	atc	ccc	ggc	ctc	aat	gtc	acg	ctg	cgc	tcg	532			
Val	Pro	Cys	Leu	Val	Ser	Ile	Pro	Gly	Leu	Asn	Val	Thr	Leu	Arg	Ser				
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caa	agc	tcg	gtg	ctg	tgg	cca	gac	ggg	cag	gag	gtg	gtg	tgg	gat	gac	580			
Gln	Ser	Ser	Val	Leu	Trp	Pro	Asp	Gly	Gln	Glu	Val	Val	Trp	Asp	Asp				
				175					180					185					
cgg	cgg	ggc	atg	ctc	gtg	tcc	acg	cca	ctg	ctg	cac	gat	gcc	ctg	tac	628			
Arg	Arg	Gly	Met	Leu	Val	Ser	Thr	Pro	Leu	Leu	His	Asp	Ala	Leu	Tyr				
				190					195					200					
ctg	cag	tgc	gag	acc	acc	tgg	gga	gac	cag	gac	ttc	ctt	tcc	aac	ccc	676			
Leu	Gln	Cys	Glu	Thr	Thr	Trp	Gly	Asp	Gln	Asp	Phe	Leu	Ser	Asn	Pro				
				205					210					215					
ttc	ctg	gtg	cac	atc	aca	ggc	aac	gag	ctc	tat	gac	atc	cag	ctg	ttg	724			
Phe																			



Cys	Thr	Val	Trp	Ala	Glu	Phe	Asn	Ser	Gly	Val	Thr	Phe	Asp	Trp	Asp	
			255					260					265			
tac	cca	ggg	aag	cag	gca	gag	cgg	ggt	aag	tgg	gtg	ccc	gag	cga	cgc	868
Tyr	Pro	Gly	Lys	Gln	Ala	Glu	Arg	Gly	Lys	Trp	Val	Pro	Glu	Arg	Arg	
		270					275					280				
tcc	cag	cag	acc	cac	aca	gaa	ctc	tcc	agc	atc	ctg	acc	atc	cac	aac	916
Ser	Gln	Gln	Thr	His	Thr	Glu	Leu	Ser	Ser	Ile	Leu	Thr	Ile	His	Asn	
	285					290					295					
gtc	agc	cag	cac	gac	ctg	ggc	tcg	tat	gtg	tgc	aag	gcc	aac	aac	ggc	964
Val	Ser	Gln	His	Asp	Leu	Gly	Ser	Tyr	Val	Cys	Lys	Ala	Asn	Asn	Gly	
300					305					310					315	
atc	cag	cga	ttt	cgg	gag	agc	acc	gag	gtc	att	gtg	cat	gaa	aat	ccc	1012
Ile	Gln	Arg	Phe	Arg	Glu	Ser	Thr	Glu	Val	Ile	Val	His	Glu	Asn	Pro	
				320					325					330		
ttc	atc	agc	gtc	gag	tgg	ctc	aaa	gga	ccc	atc	ctg	gag	gcc	acg	gca	1060
Phe	Ile	Ser	Val	Glu	Trp	Leu	Lys	Gly	Pro	Ile	Leu	Glu	Ala	Thr	Ala	
			335					340					345			
gga	gac	gag	ctg	gtg	aag	ctg	ccc	gtg	aag	ctg	gca	gcg	tac	ccc	ccg	1108
Gly	Asp	Glu	Leu	Val	Lys	Leu	Pro	Val	Lys	Leu	Ala	Ala	Tyr	Pro	Pro	
		350					355					360				
ccc	gag	ttc	cag	tgg	tac	aag	gat	gga	aag	gca	ctg	tcc	ggg	cgc	cac	1156
Pro	Glu	Phe	Gln	Trp	Tyr	Lys	Asp	Gly	Lys	Ala	Leu	Ser	Gly	Arg	His	
	365					370					375					
agt	cca	cat	gcc	ctg	gtg	ctc	aag	gag	gtg	aca	gag	gcc	agc	aca	ggc	1204
Ser	Pro	His	Ala	Leu	Val	Leu	Lys	Glu	Val	Thr	Glu	Ala	Ser	Thr	Gly	
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acc	tac	acc	ctc	gcc	ctg	tgg	aac	tcc	gct	gct	ggc	ctg	agg	cgc	aac	1252
Thr	Tyr	Thr	Leu	Ala	Leu	Trp	Asn	Ser	Ala	Ala	Gly	Leu	Arg	Arg	Asn	
				400					405					410		
atc	agc	ctg	gag	ctg	gtg	gtg	aat	gtg	ccc	ccc	cag	ata	cat	gag	aag	1300
Ile	Ser	Leu	Glu	Leu	Val	Val	Asn	Val	Pro	Pro	Gln	Ile	His	Glu	Lys	
			415					420					425			
gag	gcc	tcc	tcc	ccc	agc	atc	tac	tcg	cgt	cac	agc	cgc	cag	gcc	ctc	1348
Glu	Ala	Ser	Ser	Pro	Ser	Ile	Tyr	Ser	Arg	His	Ser	Arg	Gln	Ala	Leu	
		430					435					440				
acc	tgc	acg	gcc	tac	ggg	gtg	ccc	ctg	cct	ctc	agc	atc	cag	tgg	cac	1396
Thr	Cys	Thr	Ala	Tyr	Gly	Val	Pro	Leu	Pro	Leu	Ser	Ile	Gln	Trp	His	
	445					450					455					
tgg	cgg	ccc	tgg	aca	ccc	tgc	aag	atg	ttt	gcc	cag	cgt	agt	ctc	cgg	1444
Trp	Arg	Pro	Trp	Thr	Pro	Cys	Lys	Met	Phe	Ala	Gln	Arg	Ser	Leu	Arg	
460					465					470					475	
cgg	cgg	cag	cag	caa	gac	ctc	atg	cca	cag	tgc	cgt	gac	tgg	agg	gcg	1492
Arg	Arg	Gln	Gln	Gln	Asp	Leu	Met	Pro	Gln	Cys	Arg	Asp	Trp	Arg	Ala	
				480					485					490		
gtg	acc	acg	cag	gat	gcc	gtg	aac	ccc	atc	gag	agc	ctg	gac	acc	tgg	1540
Val	Thr	Thr	Gln	Asp	Ala	Val	Asn	Pro	Ile	Glu	Ser	Leu	Asp	Thr	Trp	

495							500					505					
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Thr	Glu	Phe	Val	Glu	Gly	Lys	Asn	Lys	Thr	Val	Ser	Lys	Leu	Val	Ile		
		510					515					520					
cag	aat	gcc	aac	gtg	tct	gcc	atg	tac	aag	tgt	gtg	gtc	tcc	aac	aag	1636	
Gln	Asn	Ala	Asn	Val	Ser	Ala	Met	Tyr	Lys	Cys	Val	Val	Ser	Asn	Lys		
		525					530				535						
gtg	ggc	cag	gat	gag	cgg	ctc	atc	tac	ttc	tat	gtg	acc	acc	atc	ccc	1684	
Val	Gly	Gln	Asp	Glu	Arg	Leu	Ile	Tyr	Phe	Tyr	Val	Thr	Thr	Ile	Pro		
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gac	ggc	ttc	acc	atc	gaa	tcc	aag	cca	tcc	gag	gag	cta	cta	gag	ggc	1732	
Asp	Gly	Phe	Thr	Ile	Glu	Ser	Lys	Pro	Ser	Glu	Glu	Leu	Leu	Glu	Gly		
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cag	ccg	gtg	ctc	ctg	agc	tgc	caa	gcc	gac	agc	tac	aag	tac	gag	cat	1780	
Gln	Pro	Val	Leu	Leu	Ser	Cys	Gln	Ala	Asp	Ser	Tyr	Lys	Tyr	Glu	His		
			575					580					585				
ctg	cgc	tgg	tac	cgc	ctc	aac	ctg	tcc	acg	ctg	cac	gat	gcg	cac	ggg	1828	
Leu	Arg	Trp	Tyr	Arg	Leu	Asn	Leu	Ser	Thr	Leu	His	Asp	Ala	His	Gly		
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aac	ccg	ctt	ctg	ctc	gac	tgc	aag	aac	gtg	cat	ctg	ttc	gcc	acc	cct	1876	
Asn	Pro	Leu	Leu	Leu	Asp	Cys	Lys	Asn	Val	His	Leu	Phe	Ala	Thr	Pro		
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ctg	gcc	gcc	agc	ctg	gag	gag	gtg	gca	cct	ggg	gcg	cgc	cac	gcc	acg	1924	
Leu	Ala	Ala	Ser	Leu	Glu	Glu	Val	Ala	Pro	Gly	Ala	Arg	His	Ala	Thr		
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ctc	agc	ctg	agt	atc	ccc	cgc	gtc	gcg	ccc	gag	cac	gag	ggc	cac	tat	1972	
Leu	Ser	Leu	Ser	Ile	Pro	Arg	Val	Ala	Pro	Glu	His	Glu	Gly	His	Tyr		
				640					645					650			
gtg	tgc	gaa	gtg	caa	gac	cgg	cgc	agc	cat	gac	aag	cac	tgc	cac	aag	2020	
Val	Cys	Glu	Val	Gln	Asp	Arg	Arg	Ser	His	Asp	Lys	His	Cys	His	Lys		
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aag	tac	ctg	tcg	gtg	cag	gcc	ctg	gaa	gcc	cct	cgg	ctc	acg	cag	aac	2068	
Lys	Tyr	Leu	Ser	Val	Gln	Ala	Leu	Glu	Ala	Pro	Arg	Leu	Thr	Gln	Asn		
			670				675					680					
ttg	acc	gac	ctc	ctg	gtg	aac	gtg	agc	gac	tcg	ctg	gag	atg	cag	tgc	2116	
Leu	Thr	Asp	Leu	Leu	Val	Asn	Val	Ser	Asp	Ser	Leu	Glu	Met	Gln	Cys		
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Leu	Val	Ala	Gly	Ala	His	Ala	Pro	Ser	Ile	Val	Trp	Tyr	Lys	Asp	Glu		
					705					710					715		
agg	ctg	ctg	gag	gaa	aag	tct	gga	gtc	gac	ttg	gcg	gac	tcc	aac	cag	2212	
Arg	Leu	Leu	Glu	Glu	Lys	Ser	Gly	Val	Asp	Leu	Ala	Asp	Ser	Asn	Gln		
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aag	ctg	agc	atc	cag	cgc	gtg	cgc	gag	gag	gat	gcg	gga	cgc	tat	ctg	2260	
Lys	Leu	Ser	Ile	Gln	Arg	Val	Arg	Glu	Glu	Asp	Ala	Gly	Arg	Tyr	Leu		
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765 770 775	
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780 785 790 795	
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800 805 810	
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815 820 825	
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830 835 840	
cgg ctg cac ctg ggg aga gtg ctc ggc tac ggc gcc ttc ggg aag gtg Arg Leu His Leu Gly Arg Val Leu Gly Tyr Gly Ala Phe Gly Lys Val	2596
845 850 855	
gtg gaa gcc tcc gct ttc ggc atc cac aag ggc agc agc tgt gac acc Val Glu Ala Ser Ala Phe Gly Ile His Lys Gly Ser Ser Cys Asp Thr	2644
860 865 870 875	
gtg gcc gtg aaa atg ctg aaa gag ggc gcc acg gcc agc gag cac cgc Val Ala Val Lys Met Leu Lys Glu Gly Ala Thr Ala Ser Glu His Arg	2692
880 885 890	
gcg ctg atg tcg gag ctc aag atc ctc att cac atc ggc aac cac ctc Ala Leu Met Ser Glu Leu Lys Ile Leu Ile His Ile Gly Asn His Leu	2740
895 900 905	
aac gtg gtc aac ctc ctc ggg gcg tgc acc aag ccg cag ggc ccc ctc Asn Val Val Asn Leu Leu Gly Ala Cys Thr Lys Pro Gln Gly Pro Leu	2788
910 915 920	
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940 945 950 955	
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960 965 970	
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975 980 985	
acc gag ggc gga gcg agg cgg gct tct cca gac caa gaa gct gag gac	3028

Thr	Glu	Gly	Gly	Ala	Arg	Arg	Ala	Ser	Pro	Asp	Gln	Glu	Ala	Glu	Asp		
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Gln	Val	Ala	Arg	Gly	Met	Glu	Phe	Leu	Ala	Ser	Arg	Lys	Cys	Ile	His		
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aga	gac	ctg	gct	gct	cgg	aac	att	ctg	ctg	tcg	gaa	agc	gac	gtg	gtg	3172	
Arg	Asp	Leu	Ala	Ala	Arg	Asn	Ile	Leu	Leu	Ser	Glu	Ser	Asp	Val	Val		
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Lys	Ile	Cys	Asp	Phe	Gly	Leu	Ala	Arg	Asp	Ile	Tyr	Lys	Asp	Pro	Asp		
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Tyr	Val	Arg	Lys	Gly	Ser	Ala	Arg	Leu	Pro	Leu	Lys	Trp	Met	Ala	Pro		
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gaa	agc	atc	ttc	gac	aag	gtg	tac	acc	acg	cag	agt	gac	gtg	tgg	tcc	3316	
Glu	Ser	Ile	Phe	Asp	Lys	Val	Tyr	Thr	Thr	Gln	Ser	Asp	Val	Trp	Ser		
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Phe	Gly	Val	Leu	Leu	Trp	Glu	Ile	Phe	Ser	Leu	Gly	Ala	Ser	Pro	Tyr		
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Thr	Arg	Met	Arg	Ala	Pro	Glu	Leu	Ala	Thr	Pro	Ala	Ile	Arg	Arg	Ile		
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gag	ctg	gtg	gag	atc	ctg	ggg	gac	ctg	ctc	cag	ggc	agg	ggc	ctg	caa	3556	
Glu	Leu	Val	Glu	Ile	Leu	Gly	Asp	Leu	Leu	Gln	Gly	Arg	Gly	Leu	Gln		
	1165					1170					1175						
gag	gaa	gag	gag	gtc	tgc	atg	gcc	ccg	cgc	agc	tct	cag	agc	tca	gaa	3604	
Glu	Glu	Glu	Glu	Val	Cys	Met	Ala	Pro	Arg	Ser	Ser	Gln	Ser	Ser	Glu		
	1180				1185					1190				1195			
gag	ggc	agc	ttc	tcg	cag	gtg	tcc	acc	atg	gcc	cta	cac	atc	gcc	cag	3652	
Glu	Gly	Ser	Phe	Ser	Gln	Val	Ser	Thr	Met	Ala	Leu	His	Ile	Ala	Gln		
			1200						1205					1210			
gct	gac	gct	gag	gac	agc	ccg	cca	agc	ctg	cag	cgc	cac	agc	ctg	gcc	3700	
Ala	Asp	Ala	Glu	Asp	Ser	Pro	Pro	Ser	Leu	Gln	Arg	His	Ser	Leu	Ala		
			1215					1220					1225				
gcc	agg	tat	tac	aac	tgg	gtg	tcc	ttt	ccc	ggg	tgc	ctg	gcc	aga	ggg	3748	
Ala	Arg	Tyr	Tyr	Asn	Trp	Val	Ser	Phe	Pro	Gly	Cys	Leu	Ala	Arg	Gly		

1230	1235	1240	
gct gag acc cgt ggt tcc tcc agg atg aag aca ttt gag gaa ttc ccc			3796
Ala Glu Thr Arg Gly Ser Ser Arg Met Lys Thr Phe Glu Glu Phe Pro			
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Organization  
International Bureau



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10 April 2003 (10.04.2003)

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- (21) International Application Number: **PCT/EP2002/011069**
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60/326,326 1 October 2001 (01.10.2001) US
- (71) Applicants (for all designated States except US): **LUDWIG INSTITUTE FOR CANCER RESEARCH** [US/US]; 605 Third Avenue, New York, NY 10158 (US). **LICENTIA LTD** [FI/FI]; Erottajankatu 19B, 6th Floor, FIN-00130 Helsinki (FI).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **ALITALO, Karl** [FI/FI]; Molecular Cancer Biology Laboratory, Biomedicum, Helsinki, Haartmaninkatu 8, FIN-00014 Helsinki (FI). **KARKKAINEN, Marika** [FI/FI]; Molecular Cancer Biology Laboratory, Biomedicum, Helsinki, Haartmaninkatu 8, FIN-00014 Helsinki (FI). **KARILA, Kaisa** [FI/NL]; Merelstraat 40, NL-2333 XM Leiden (NL).
- (74) Agents: **JUMP, Timothy et al.**; Venner, Shipley & Co., 20 Little Britain, London EC1A 7DH (GB).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:  
— with international search report  
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- (88) Date of publication of the international search report:  
31 December 2003
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2003/029814 A3

(54) Title: **NEUROPILIN/VEGF C/VEGFR 3 MATERIALS AND METHODS**

(57) Abstract: The present invention relates to identifying modulators of VEGF-C or VEGF-D ligand binding to the nervous system transmembrane protein neuropilin-2 and materials and methods for detecting said modulators.

## INTERNATIONAL SEARCH REPORT

In Application No

PCT/EP 02/11069

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 G01N33/50 G01N33/74 C07K16/46 C07K14/475

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 G01N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 23565 A (LUDWIG INSTITUTE FOR CANCER RESEARCH) 27 April 2000 (2000-04-27)  page 1 - page 11 claims 4-21  -----	1-18, 26-30, 33-38
Y	WO 99 29729 A (CHILDREN'S MEDICAL CENTER CORPORATION) 17 June 1999 (1999-06-17)  the whole document  -----	1-18, 26-30, 33-38
Y	WO 01 09157 A (NEXSTAR PHARMACEUTICALS, INC.) 8 February 2001 (2001-02-08)  page 1, line 20 - page 8, line 20  -----  -/--	1-18, 26-30, 33-38

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"A" document member of the same patent family

Date of the actual completion of the international search

11 July 2003

Date of mailing of the international search report

03.11.03

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Giry, M.

## INTERNATIONAL SEARCH REPORT

Int I Application No.

PCT/EP 02/11069

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 07832 A (LUDWIG INSTITUTE FOR CANCER RESEARCH) 26 February 1998 (1998-02-26)  claims 37-77; example 7 -----	1-18, 26-30, 33-38
Y	WO 01 31346 A (PROCTER & GAMBLE COMPANY) 3 May 2001 (2001-05-03) page 1, line 5 - page 6, line 21 page 12, line 25 - page 13, line 33 example 7 claims 1-11 -----	16,17
Y	WO 00 21560 A (LUDWIG INSTITUTE FOR CANCER RESEARCH) 20 April 2000 (2000-04-20) page 83, line 19 - page 84, line 14 examples 15-17 -----	12,13, 16,17
Y	page 87, line 10 - line 20 -----	29,30
A	ACHEN M.G. ET AL.: "Monoclonal antibodies to vascular endothelial growth factor-D block its interactions with both VEGF receptor-2 and VEGF receptor-3." EUR. J. BIOCHEM., vol. 267, 2000, pages 2505-2515, XP002247239 the whole document -----	
A	BAGNARD D. ET AL.: "Semaphorin 3A-vascular endothelial growth factor-165 balance mediates migration and apoptosis of neural progenitor cells by the recruitment of shared receptor." J. NEUROSC., vol. 21, no. 10, 15 May 2001 (2001-05-15), pages 3332-3341, XP001057926 the whole document -----	
P,X	KARKKAINEN M.J. ET AL.: "Lymphatic endothelium : a new frontier of metastasis research." NATURE CELL BIOLOGY, vol. 4, January 2002 (2002-01), pages E2-E5, XP002247240 the whole document -----	1-18, 26-30, 33-38

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 02/11069

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 3, 26-29, 33-37  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 3, 26-29, and 33-37, due to the step of administering a composition, are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1-18, 26-30, 33-38

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 3, 26-29, 33-37

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-18, 26-30, 33-38

Methods and peptidic compounds relating to the ability of VEGF-C to bind to neuropilin.

---

2. claims: 19-25, 31-32

Methods and peptidic compounds relating to the ability of VEGFR-3 to bind to neuropilin.

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/11069

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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			NO 20011759 A	11-06-2001
			WO 02060950 A2	08-08-2002
			WO 0021560 A1	20-04-2000



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Organization  
International Bureau



(43) International Publication Date  
10 April 2003 (10.04.2003)

PCT

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**WO 2003/029814 A3**

(51) International Patent Classification<sup>7</sup>: **G01N 33/50**,  
33/74, C07K 16/46, 14/475

(74) Agents: JUMP, Timothy et al.; Venner, Shipley & Co., 20  
Little Britain, London EC1A 7DH (GB).

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(22) International Filing Date: 1 October 2002 (01.10.2002)

(25) Filing Language: English

(26) Publication Language: English

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AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,  
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,  
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,  
VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,  
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(54) Title: NEUROPILIN/VEGF C/VEGFR 3 MATERIALS AND METHODS

(57) Abstract: The present invention relates to identifying modulators of VEGF-C or VEGF-D ligand binding to the nervous system transmembrane protein neuropilin-2 and materials and methods for detecting said modulators.

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## AMENDED CLAIMS

[received by the International Bureau on 02 January 2004 (02.01.04) ;  
original claims 1-38 replaced by amended claims 1-37 (9 pages)]

What is claimed is:

1. A method of screening for modulators of binding between a neuropilin-2 growth factor receptor and a VEGF-C polypeptide, comprising steps of:

a) contacting a neuropilin-2 composition that comprises a neuropilin-2 polypeptide with a VEGF-C composition that comprises a VEGF-C polypeptide, in the presence and in the absence of a putative modulator compound;

b) detecting binding between the neuropilin-2 polypeptide and the VEGF-C polypeptide in the presence and absence of the putative modulator compound; and

c) identifying a modulator compound based on a decrease or increase in binding between the neuropilin-2 polypeptide and the VEGF-C polypeptide in the presence of the putative modulator compound, as compared to binding in the absence of the putative modulator compound.

2. A method according to claim 1, further comprising a step of:

(d) making a modulator composition by formulating a modulator identified according to step (c) in a pharmaceutically acceptable carrier.

3. A method according to claim 2, further comprising:

(e) administering the modulator composition to an animal that comprises cells that express the neuropilin-2 receptor, and determining physiological effects of the modulator composition in the animal.

4. A method according to any one of claims 1-3 wherein the neuropilin-2 composition comprises a member selected from the group consisting of:

(a) a purified polypeptide comprising a neuropilin-2 receptor extracellular domain that binds VEGF-C;

(b) a phospholipid membrane containing neuropilin-2 polypeptides;  
and

(c) a cell recombinantly modified to express increased levels of

neuropilin-2 receptor polypeptide on the cell surface.

5. A method according to any one of claims 1-3, wherein the neuropilin-2 composition comprises a polypeptide comprising a neuropilin-2 receptor extracellular domain fragment bound to a solid support.

6. A method according to claim 1, wherein the neuropilin-2 polypeptide comprises a neuropilin-2 receptor extracellular domain fragment fused to an immunoglobulin Fc fragment.

7. A method according to any one of claims 1-6, wherein the neuropilin-2 polypeptide is human.

8. A method according to any one of claims 1-6 wherein the neuropilin-2 polypeptide comprises an amino acid sequence at least 90% identical to: the amino acid sequence set forth in SEQ ID NO: 4 or a fragment thereof that binds VEGF-C.

9. A method according to any one of claims 1-8 wherein the VEGF-C polypeptide comprises a purified mammalian prepro-VEGF-C polypeptide or a fragment of the prepro-VEGF-C polypeptide, that binds the neuropilin-2 receptor.

10. A method according to claim 9, wherein the prepro-VEGF-C polypeptide is human.

11. A method according to any one of claims 1-8 wherein the VEGF-C polypeptide comprises an amino acid sequence at least 90% identical to: the amino acid sequence set forth in SEQ ID NO: 24 or a fragment thereof that binds neuropilin-2.

12. A method according to any one of claims 1-8, wherein the VEGF-C polypeptide comprises a fragment of human prepro-VEGF-C that contains amino acids 103-227 of SEQ ID NO: 24.

13. A method according to any one of claims 1-8, wherein the VEGF-C polypeptide comprises amino acids 32 to 227 of the human prepro-VEGF-C sequence of SEQ. ID. NO: 24.

14. A method according to any one of claims 1-8, wherein the VEGF-C composition comprises a conditioned media from a cell recombinantly modified to express and secrete a VEGF-C polypeptide.

15. A method according to any one of claims 1-3, wherein the neuropilin-2 composition comprises a cell recombinantly modified to express increased amounts of a neuropilin-2 receptor on its surface, and wherein the detecting step comprises measuring a VEGF-C binding-induced physiological change in the cell.

16. A method for screening for selectivity of a modulator of VEGF-C biological activity, comprising steps of:

a) contacting a VEGF-C composition with a neuropilin-2 composition in the presence and in the absence of a compound and detecting binding between the VEGF-C and the neuropilin-2 in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the VEGF-C and the neuropilin-2;

b) contacting a VEGF-C composition with a composition comprising a VEGF-C binding partner in the presence and in the absence of the compound and detecting binding between the VEGF-C and the binding partner in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the VEGF-C and the binding partner; and wherein the binding partner is selected from the group consisting of:

(i) a polypeptide comprising a VEGFR-3 extracellular domain; and

- (ii) a polypeptide comprising a VEGFR-2 extracellular domain; and
- (c) identifying the selectivity of the modulator compound in view of the binding detected in steps (a) and (b).

17. A method for screening for selectivity of a modulator of neuropilin-2 biological activity, comprising steps of:

a) contacting a neuropilin-2 composition with a VEGF-C composition in the presence and in the absence of a compound and detecting binding between the neuropilin-2 and the VEGF-C in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the neuropilin-2 and the VEGF-C;

b) contacting a neuropilin-2 composition with a composition comprising a neuropilin-2 binding partner in the presence and in the absence of the compound and detecting binding between the neuropilin-2 and the binding partner in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the neuropilin-2 and the binding partner; and wherein the binding partner is a polypeptide comprising an amino acid sequence selected from the group consisting of:

an amino acid sequence of a semaphorin 3 polypeptide; a VEGF-A amino acid sequence, a VEGF-B amino acid sequence, a VEGF-D amino acid sequence, a PlGF-2 amino acid sequence, a VEGFR-1 amino acid sequence, a VEGFR-2 amino acid sequence, a VEGFR-3 amino acid sequence; and an amino acid sequence of a plexin polypeptide; and

c) identifying the selectivity of the modulator compound in view of the binding detected in steps (a) and (b).

18. A method according to claim 17 wherein the binding partner is a human semaphorin.

19. A method of screening for modulators of binding between a neuropilin growth factor receptor and a VEGFR-3 polypeptide comprising steps of:

- a) contacting a neuropilin composition with a VEGFR-3 composition in the presence and in the absence of a putative modulator compound;
- b) detecting binding between the neuropilin and the VEGFR-3 in the presence and absence of the putative modulator compound; and
- c) identifying a modulator compound based on a decrease or increase in binding between the neuropilin composition and the VEGFR-3 composition in the presence of the putative modulator compound, as compared to binding in the absence of the putative modulator compound.

20. A method according to claim 19 wherein the VEGFR-3 composition comprises a member selected from the group consisting of:

- (a) a purified polypeptide comprising a VEGFR-3 receptor extracellular domain that binds VEGF-C;
- (b) a phospholipid membrane containing VEGFR-3 polypeptides; and
- (c) a cell recombinantly modified to express increased levels of VEGFR-3 receptor on the cell surface.

21. A method according to claim 19, wherein the VEGFR-3 composition comprises a VEGFR-3 extracellular domain fragment bound to a solid support.

22. A method according to claim 19, wherein the VEGFR-3 composition comprises a VEGFR-3 extracellular domain fragment fused to an immunoglobulin Fc fragment.

23. A method according to any one of claims 19-22, wherein the VEGFR-3 is a mammalian VEGFR-3.

24. A method according to claim 23, wherein the VEGFR-3 is human.

25. A method for screening for selectivity of a modulator of VEGFR-3 biological activity, comprising steps of:

a) contacting a VEGFR-3 composition with a neuropilin composition in the presence and in the absence of a compound and detecting binding between the VEGFR-3 and the neuropilin in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the VEGFR-3 and the neuropilin;

b) contacting a VEGFR-3 composition with a composition comprising a VEGFR-3 binding partner in the presence and in the absence of the compound and detecting binding between the VEGFR-3 and the binding partner in the presence and absence of the compound, wherein differential binding in the presence and absence of the compound identifies the compound as a modulator of binding between the VEGFR-3 and the binding partner; and wherein the binding partner is selected from the group consisting of:

(i) a polypeptide comprising a VEGF-C polypeptide; and

(ii) a polypeptide comprising a VEGF-D polypeptide; and

c) identifying the selectivity of the modulator compound in view of the binding detected in steps (a) and (b).

26. A method of modulating growth, migration, or proliferation of cells in a mammalian organism, comprising a step of:

(a) identifying a mammalian organism having cells that express a neuropilin-2 receptor; and

(b) administering to said mammalian organism a composition, said composition comprising a neuropilin-2 polypeptide or fragment thereof that binds to VEGF-C polypeptide expressed in the mammalian organism;

wherein the composition is administered in an amount effective to modulate growth, migration, or proliferation of cells that express neuropilin-2 in the mammalian organism.

27. A method according to claim 26, wherein the mammalian organism is human.

28. A method according to claim 26, further comprising administering a second agent to the patient for modulating endothelial growth, migration, or proliferation through a neuropilin-2 receptor, said second agent comprising a polypeptide comprising an amino acid sequence selected from the group consisting of: a VEGF-A amino acid sequence, a VEGF-B amino acid sequence, a VEGF-D amino acid sequence, a VEGF-E amino acid sequence, a PlGF amino acid sequence, a semaphorin 3A amino acid sequence, semaphorin 3C amino acid sequence, and a semaphorin 3F amino acid sequence.

29. A method of modulating growth, migration, or proliferation of cells in a mammalian organism, comprising steps of:

(a) identifying a mammalian organism having cells that express a neuropilin-2 receptor; and

(b) administering to said mammalian organism a composition, said composition comprising a bispecific antibody specific for the neuropilin-2 receptor and for a VEGF-C polypeptide expressed in the mammalian organism,

wherein the composition is administered in an amount effective to modulate growth, migration, or proliferation of cells that express the neuropilin-2 receptor in the mammalian organism.

30. A bispecific antibody which specifically binds to a neuropilin-2 receptor and a VEGF-C polypeptide.



31. A method of modulating growth, migration, or proliferation of cells in a mammalian organism, comprising steps of:

(a) identifying a mammalian organism having cells that express a neuropilin receptor and a VEGFR-3 polypeptide; and

(b) administering to said mammalian organism a composition, said composition comprising a bispecific antibody specific for the neuropilin receptor and the VEGFR-3 polypeptide,

wherein the composition is administered in an amount effective to modulate growth, migration, or proliferation of cells that express the neuropilin receptor and the VEGFR-3 polypeptide in the mammalian organism.

32. A bispecific antibody which specifically binds to a neuropilin receptor and a VEGFR-3 polypeptide.

33. A method of modulating neuronal growth, or neuronal scarring in a mammalian organism, comprising a step of:

(a) identifying a mammalian organism having cells that express a neuropilin-2 receptor; and

(b) administering to said mammalian organism a composition, said composition comprising a VEGF-C polypeptide or fragment thereof that binds to the neuropilin-2 receptor.

34. A method according to claim 33, wherein the mammalian organism is human.

35. A method according to any one of claims 33-34, wherein the organism has a disease characterized by aberrant growth of neuronal cells involved in scarring and neural degeneration.

36. A method according to claim 35, wherein the disease comprises a neurodegenerative disorder, more specifically Alzheimer's disease.

37. A polypeptide comprising a VEGF-C polypeptide or a fragment thereof that binds to a neuropilin-2 receptor, for use in the manufacture of a medicament for the treatment of diseases characterized by aberrant growth, migration, or proliferation of cells that express a neuropilin-2 receptor.